(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068984 A2

(51) International Patent Classification[7]: C12Q 1/42

(21) International Application Number: PCT/EP03/01446

(22) International Filing Date: 13 February 2003 (13.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/356,810 13 February 2002 (13.02.2002) US
10/366,547 12 February 2003 (12.02.2003) US

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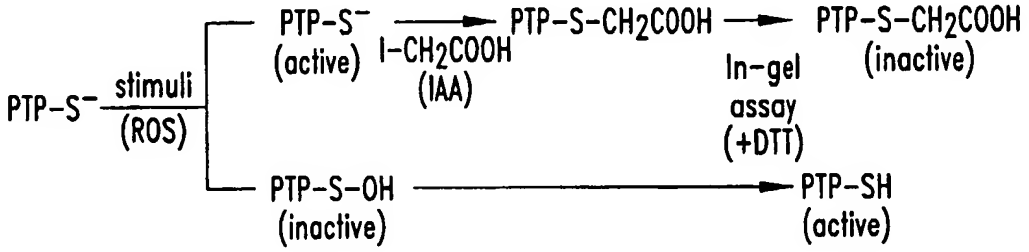
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: REVERSIBLE OXIDATION OF PROTEIN TYROSINE PHOSPHATASES




(57) Abstract: The invention relates to a method of identifying any protein tyrosine phosphatase (PTP) that undergoes reversible modification of PTP active site invariant cysteine within a cell, such that the phosphatase is transiently protected from irreversible active site invariant cysteine-directed PTP inactivating agents. Methods related to regulation of PTPs by reactive oxygen species (ROS) in a cellular environment are provided. Multiple PTPs are shown to be reversibly oxidized and inactivated following treatment of cells with HZOZ or with physiological stimuli that promote ROS formation, and inhibition of PTP function is shown to contribute to ROSinduced mitogenesis. Transient oxidation of the PTP catalytic site invariant cysteine is exploited in methods to identify which of multiple candidate PTPs are components of a given biological signal transduction pathway, without a requirement for first specifically purifying any particular candidate PTP.

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# REVERSIBLE OXIDATION OF PROTEIN TYROSINE PHOSPHATASES

## CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application No. 60/356,810 filed February 13, 2002, which is incorporated herein by reference in its entirety.

## STATEMENT OF GOVERNMENT INTEREST

The United States government may have certain rights in this invention under grant number R01-GM55989 from the National Institutes of Health.

## BACKGROUND OF THE INVENTION

The present invention relates generally to compositions and methods useful for treating conditions associated with defects in cell proliferation, cell differentiation and/or cell survival. The invention is more particularly related to identifying protein tyrosine phosphatases (PTPs) that are reversibly modified, including PTPs that are reversibly oxidized components of inducible biological signaling pathways.

Reversible protein tyrosine phosphorylation, coordinated by the action of protein tyrosine kinases (PTKs) that phosphorylate certain tyrosine residues in polypeptides, and protein tyrosine phosphatases (PTPs) that dephosphorylate certain phosphotyrosine residues, is a key mechanism in regulating many cellular activities. It is becoming apparent that the diversity and complexity of the PTPs and PTKs are comparable, and that PTPs are equally important in delivering both positive and negative signals for proper function of cellular machinery. Regulated tyrosine phosphorylation contributes to specific pathways for biological signal transduction, including those associated with cell division, cell survival, apoptosis, proliferation and differentiation. Defects and/or malfunctions in these pathways may underlie certain disease conditions for which effective means for intervention remain elusive, including for example, malignancy, autoimmune disorders, diabetes, obesity and infection.

The protein tyrosine phosphatase (PTP) family of enzymes consists of more than 500 structurally diverse proteins that have in common the highly conserved 250 amino acid PTP catalytic domain, but which display considerable variation in their non-catalytic segments (Charbonneau and Tonks, 1992 *Annu. Rev. Cell Biol. 8*:463-493; Tonks, 1993 *Semin. Cell Biol. 4*:373-453). This structural diversity presumably reflects the diversity of physiological roles of individual PTP family members, which in certain cases have been demonstrated to have specific functions in growth, development and differentiation (Desai et al., 1996 *Cell 84*:599-609; Kishihara et al., 1993 *Cell 74*:143-156; Perkins et al., 1992 *Cell 70*:225-236; Pingel and Thomas, 1989 *Cell 58*:1055-1065; Schultz et al., 1993 *Cell 73*:1445-1454; Fukada et al., 1999 *Growth Factors* 17:81-91; Gutch et al., 1998 *Genes Dev.* 12:571-85; Marengere et al., 1996 *Science* 272:1170-73). PTPs participate in a variety of physiologic functions, providing a number of opportunities for therapeutic intervention in physiologic processes through alteration (*i.e.*, a statistically significant increase or decrease) or modulation (*e.g.*, up-regulation or down-regulation) of PTP activity. For example, therapeutic inhibition of PTPs such as PTP1B in the insulin signaling pathway may serve to augment insulin action, thereby ameliorating the state of insulin resistance common in Type II diabetes patients.

Although recent studies have also generated considerable information regarding the structure, expression and regulation of PTPs, the nature of many tyrosine phosphorylated substrates through which the PTPs exert their effects remains to be determined. Studies with a limited number of synthetic phosphopeptide substrates have demonstrated some differences in the substrate selectivities of different PTPs (Cho et al., 1993 *Protein Sci. 2*: 977-984; Dechert et al., 1995 *Eur. J. Biochem. 231*:673-681). Analyses of PTP-mediated dephosphorylation of PTP substrates suggest that catalytic activity may be favored by the presence of certain amino acid residues at specific positions in the substrate polypeptide relative to the phosphorylated tyrosine residue (Salmeen et al., 2000 *Molecular Cell* 6:1401; Myers et al., 2001 *J. Biol. Chem.* 276:47771; Myers et al., 1997 *Proc. Natl. Acad. Sci. USA* 94:9052; Ruzzene et al., 1993 *Eur. J. Biochem. 211*:289-295; Zhang et al., 1994 *Biochemistry 33*:2285-2290). Thus,

although the physiological relevance of the substrates used in these studies is unclear, PTPs display a certain level of substrate selectivity *in vitro*.

The PTP family of enzymes contains a common evolutionarily conserved segment of approximately 250 amino acids known as the PTP catalytic domain. Within this conserved domain is a unique signature sequence motif,

[I/V]HCXAGXXR[S/T]G SEQ ID NO:98,

that is invariant among all PTPs. The cysteine residue in this motif is invariant in members of the family and is known to be essential for catalysis of the phosphotyrosine dephosphorylation reaction. It functions as a nucleophile to attack the phosphate moiety present on a phosphotyrosine residue of the incoming substrate. If the cysteine residue is altered by site-directed mutagenesis to serine (*e.g.*, in cysteine-to-serine or "CS" mutants) or alanine (*e.g.*, cysteine-to-alanine or "CA" mutants), the resulting PTP is catalytically deficient but retains the ability to complex with, or bind, its substrate, at least *in vitro*.

CS mutants of certain PTP family members, for example, MKP-1 (Sun et al., 1993 *Cell* 75:487), may effectively bind phosphotyrosyl polypeptide substrates in vitro to form stable enzyme-substrate complexes, thereby functioning as "substrate trapping" mutant PTPs. Such complexes can be isolated from cells in which both the mutant PTP and the phosphotyrosyl polypeptide substrates are present. According to non-limiting theory, expression of such a CS mutant PTP can thus antagonize the normal function of the corresponding wildtype PTP (and potentially other PTPs and/or other components of a PTP signaling pathway) via a mechanism whereby the CS mutant binds to and sequesters the substrate, precluding substrate interaction with catalytically active, wildtype enzyme (*e.g.*, Sun et al., 1993).

CS mutants of certain other PTP family members, however, may bind phosphotyrosyl polypeptide substrates and form complexes that exist transiently and are not stable when the CS mutant is expressed in cells, *i.e., in vivo*. The CS mutant of PTP1B is an example of such a PTP. Catalytically deficient mutants of such enzymes that are capable of forming stable complexes with phophotyrosyl polypeptide substrates

may be derived by mutating a wildtype protein tyrosine phosphatase catalytic domain invariant aspartate residue and replacing it with an amino acid that does not cause significant alteration of the Km of the enzyme but that results in a reduction in Kcat, as disclosed, for example, in U.S. Patent Nos. 5,912,138 and 5,951,979, in U.S. Application No. 09/323,426 and in PCT/US97/13016. For instance, mutation of Asp 181 in PTP1B to alanine to create the aspartate-to-alanine (D to A or DA) mutant PTP1B-D181A results in a PTP1B "substrate trapping" mutant enzyme that forms a stable complex with its phosphotyrosyl polypeptide substrate (*e.g.*, Flint et al., 1997 *Proc. Nat. Acad. Sci. USA* 94:1680). Substrates of other PTPs can be identified using a similar substrate trapping approach, for example substrates of the PTP family members PTP-PEST (Garton et al., 1996 *J. Mol. Cell. Biol.* 16:6408), TCPTP (Tiganis et al., 1998 *Mol. Cell Biol.* 18:1622), PTP-HSCF (Spencer et al., 1997 *J. Cell Biol.* 138:845) and PTP-H1 (Zhang et al., 1999 *J. Biol. Chem.* 274:17806).

Mitogen-activated protein kinases (MAP-kinases) are present as components of conserved cellular signal transduction pathways that have a variety of conserved members. MAP-kinases are activated by phosphorylation at a dual phosphorylation motif with the sequence Thr-X-Tyr (by MAP-kinase kinases), in which phosphorylation at the tyrosine and threonine residues is required for activity. Activated MAP-kinases phosphorylate several transduction targets, including transcription factors. Inactivation of MAP-kinases is mediated by dephosphorylation at this site by dual-specificity phosphatases referred to as MAP-kinase phosphatases. In higher eukaryotes, the physiological role of MAP-kinase signaling has been correlated with cellular events such as proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to the development of treatments and preventive therapies for human diseases associated with MAP-kinase signaling, such as cancer.

Dual-specificity protein tyrosine phosphatases (dual-specificity phosphatases) are phosphatases that dephosphorylate both phosphotyrosine and phosphothreonine/serine residues (Walton et al., *Ann. Rev. Biochem.* 62:101-120, 1993). Several dual-specificity phosphatases that inactivate a MAP-kinase have been identified, including MKP-1 (WO 97/00315; Keyse and Emslie, *Nature 59*:644-647,

1992), MKP-2 (WO97/00315), MKP-4, MKP-5, MKP-7, Hb5 (WO 97/06245), PAC1 (Ward et al., *Nature 367*:651-654, 1994), HVH2 (Guan and Butch, *J. Biol. Chem. 270*:7197-7203, 1995) and PYST1 (Groom et al., *EMBO J. 15*:3621-3632, 1996). Expression of certain dual-specificity phosphatases is induced by stress or mitogens, but others appear to be expressed constitutively in specific cell types. The regulation of dual-specificity phosphatase expression and activity is critical for control of MAP-kinase mediated cellular functions, including cell proliferation, cell differentiation and cell survival. For example, dual-specificity phosphatases may function as negative regulators of cell proliferation. It is likely that there are many such dual-specificity phosphatases, with varying specificity with regard to cell type or activation. However, the regulation of dual specificity phosphatases remains poorly understood and only a relatively small number of dual-specificity phosphatases have been identified.

Currently, desirable goals for determining the molecular mechanisms that govern PTP-mediated cellular events include, *inter alia*, determination of PTP interacting molecules, substrates and binding partners, and identification of agents that regulate PTP activities. In some situations, however, current approaches may lead to an understanding of certain aspects of the regulation of tyrosine phosphorylation by PTPs, but still may not provide strategies to control specific tyrosine phosphorylation and/or dephosphorylation events within a cell. Accordingly, there is a need in the art for an improved ability to manipulate phosphotyrosine signaling, including intervention in the regulation of PTPs. An increased understanding of PTP regulation may facilitate the development of methods for modulating the activity of proteins involved in phosphotyrosine signaling pathways, and for treating conditions associated with such pathways.

Hence, and as also noted above, over the last fifteen years it has been established that the Protein Tyrosine Phosphatases (PTPs) are a large, structurally diverse family of receptor-like and non-transmembrane enzymes, which exhibit exquisite substrate specificity *in vivo* and are critical regulators of a wide array of cellular signaling pathways (Andersen et al., 2001 *Mol. Cell. Biol.* 21:7117; Tonks and Neel, 2001 *Curr. Opin. Cell Biol.* 13:182). An important area of investigation in the field remains the characterization of mechanisms by which the activity of the PTPs

themselves may be regulated *in vivo*. Recently, the proposal that certain PTPs may be susceptible to oxidation and inactivation has introduced an additional tier of complexity to the regulation of this family of enzymes.

It is now apparent that reactive oxygen species (ROS) are not merely a harmful by-product of life in an aerobic environment. The importance of ROS in phagocytic cells, such as neutrophils, is well documented. Various stimuli lead to the assembly of a multi-component NADPH oxidase complex, which mediates a process known as the respiratory burst (DeLeo et al., 1996 *J. Leukoc. Biol.* 60:677). NADPH oxidase catalyses transfer of one electron from NADPH to molecular oxygen to generate superoxide anions, which in turn may yield hydrogen peroxide, either via protonation of superoxide or through the action of superoxide dismutase (Thelen et al., 1993 *Physiol. Rev.* 73:797). The large quantities of such ROS produced in phagocytic cells have been implicated as microbicidal agents and in certain pathological situations can result in host cell damage (Smith et al., 1991 *Blood* 77:673). However, many recent studies have revealed that the production of ROS is tightly regulated, engendering the concept that, at lower levels than those generated for a microbicidal function, ROS may also function in propagating a signaling response to extracellular stimuli (Finkel, 1998 *Curr. Opin. Cell Biol.* 10:248; Finkel, 2000 *FEBS Lett.* 476:52). Thus, in a manner analogous to reversible protein phosphorylation, the reversible oxidation of target proteins in a cell may regulate the function of those proteins in response to various agonists and thus elicit a cellular response to stimulation (Finkel, 1998).

Several lines of investigation have implicated ROS in the regulation of mitogenic signaling in mammalian cells (Adler et al., 1999 *Oncogene* 18:6104; Brummel et al., 1996 *J. Biol. Chem.* 271:1455-61; Chen et al., 1995 *J. Biol. Chem.* 270:28499; Sundaresan et al., 1995 *Science* 270:296). Mild oxidation can yield a stable sulfenic acid modification of cysteine residues (Cys-SOH) in selected proteins, including a variety of enzymes and transcription factors, which has the potential to regulate the function of those proteins (Claiborne et al., 1999 *Biochemistry* 38:15407). In order to understand the role of ROS and redox regulation in the control of signal transduction, it is particularly important to identify the targets of reversible oxidation *in*

*vivo*. In this context, attention has been drawn to the PTPs, which together with the PTKs are responsible for maintaining a normal tyrosine phosphorylation status *in vivo*. As described above, the PTPs are characterized by a signature motif, I/V-H-C-X-X-G-X-X-R-S/T, which forms the base of the active site cleft and contains an invariant Cys residue (Barford et al., 1995 *Nat. Struct. Biol.* 2:1043). The catalytic mechanism involves a two-step process, commencing with nucleophilic attack by the Sγ atom of the catalytic Cys on the phosphorus atom of the phosphotyrosyl substrate, resulting in formation of a phospho-Cys intermediate. In the second step the transient phospho-enzyme intermediate is hydrolyzed by an activated water molecule (Barford et al., 1995). Due to the unusual environment of the PTP active site, the pKα of the sulfhydryl group of this Cys residue is extremely low (~5.4 in PTP1B, (Lohse et al., 1997 *Biochemistry* 36:4568) and ~4.7 in YOP, (Zhang et al., 1993 *Biochemistry* 32:9340)) compared to the typical pKα for Cys (~8.5), which favors its function as a nucleophile but renders it susceptible to oxidation. It has now been shown *in vitro* that treatment with $H_2O_2$ of various PTPs (Lee et al., 1998 *J. Biol. Chem.* 273:15366), dual specificity phosphatses (Denu et al., 1998 *Biochemistry* 37:5633) and low molecular weight PTPs (Caselli et al., 1998 *J. Biol. Chem.* 273:32554) leads to oxidation of the active site Cys to sulfenic acid. Such oxidation results in inhibition of activity, because the modified Cys can no longer function as a phosphate acceptor in the first step of the PTP-catalyzed reaction.

Oxidation of Cys to sulfenic acid is reversible (Claiborne et al., 1999 *Biochemistry* 38:15407) and thus has the potential to form the basis of a mechanism for reversible regulation of PTP activity. In contrast, oxidation by the addition of 2 (sulfinic acid) or 3 (sulfonic acid) oxygens to the active site Cys is irreversible. Interestingly, glutathionylation of the sulfenic acid form of PTP1B has been reported (Barrett et al., 1999 *Biochemistry* 38:6699) and proposed as a mechanism to protect against further, irreversible oxidation and as an important step in the reverse, reduction mechanism. Stimulation of A431 cells with EGF was also shown to lead to the production of $H_2O_2$ and concomitant inhibition of PTP1B (Bae et al., 1997 *J. Biol. Chem.* 272:217). Increased production of intracellular oxidants may contribute to enhanced, tyrosine phosphorylation-dependent signaling, for example in response to

growth factors (Bae et al., 1997; Bae et al., 2000 *J. Biol. Chem.* 275:10527; Sundaresan et al., 1995 *Science* 270:296), by transiently suppressing the enzymatic activity of members of the PTP family, thereby promoting a burst of PTK activity (Finkel, 1998; 2000).

However, it is unclear how broadly this phenomenon may apply across the PTP family, and methods have not previously been available for assessing potential reversible oxidation in a broad range of PTPs in a cellular context, *i.e.*, within a living cell, or *in vivo*. In particular, there is a need for a method by which one or more oxidized/inactivated PTPs in a cell could be distinguished from reduced/activated PTPs in the cell, and in a manner which need not be specific for a particular PTP, or which need not require that each PTP being investigated be highly purified (*e.g.*, specifically immunoprecipitated) or recombinantly cloned and expressed. An increased understanding of PTP regulation in biological signal transduction, including via inducible signaling pathways triggered by biological stimuli, may facilitate the development of methods for modulating the activity of proteins involved in PTK/PTP cascades, and for treating conditions associated with such cascades. The present invention fulfills these needs and further provides other related advantages.

## SUMMARY OF THE INVENTION

It is an aspect of the present invention to provide a method for identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus under conditions and for a time sufficient to induce reversible oxidation of at least one protein tyrosine phosphatase in the cell; isolating anaerobically the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and

therefrom identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell. In one embodiment, the invention provides a method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2 in the cell; isolating anaerobically SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell. In another embodiment, the invention provides a method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell; isolating anaerobically PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell. In certain other embodiments of the present invention, a method is provided for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45 in the cell; isolating anaerobically TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate

by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell.

In certain embodiments the protein tyrosine phosphatase is PTP1B, PTP-PEST, PTPγ, LAR, MKP-1, CRYPα, PTPcryp2, DEP-1, SAP1, PCPTP1, PTPSL, STEP, HePTP, PTPIA2, PTPNP, PTPNE6, PTPμ, PTPX1, PTPX10, SHP-1, SHP-2, PTPBEM1, PTPBEM2, PTPBYP, PTPesp, PTPoc, PTP-PEZ, PTP-MEG1, MEG2, LC-PTP, TC-PTP, TC45, CD45, LAR, cdc14, RPTP-α, RPTP-ε, RKPTP, LyPTP, PEP, BDP1, PTP20, PTPK1, PTPS31, PTPGMC, GLEPP1, OSTPTP, PTPtep, PTPRL10, PTP2E, PTPD1, PTPD2, PTP36, PTPBAS, PTPBL, BTPBA14, PTPTyp, HDPTP, PTPTD14, PTPα, PTPβ, PTPδ, PTPε, PTPκ, PTPλ, PTPμ, PTPρ, PTPψ, PTPϕ, PTPζ, PTPNU3 or PTPH1, or a PTP as presented in Figure 8, or a dual specificity phosphatase including but not limited to PYST-1, MKP-1, MKP-2, MKP-4, MKP-5, MKP-7, hVH5, PAC1, VHR, or any dual specificity phosphatase disclosed in WO00/65069 (DSP-5), WO00/65068 (DSP-10), WO00/63393 (DSP-8), WO00/60100 (DSP-9), WO00/60099 (DSP-4), WO00/60098 (DSP-7), WO00/60092 (DSP-3), WO00/56899 (DSP-2), WO00/53636 (DSP-1), WO00/09656 (MKP), AU5475399 (MKP), AU8479498, WO99/02704, WO97/06245 (MKP), WO01/83723, WO01/57221, WO01/05983, WO01/02582, WO01/02581, U.S.A.N. 09/955,732 (DSP-15), U.S.A.N. 09/964,277 (DSP-16), U.S.A.N. 60/268,837 (DSP-17) or U.S.A.N. 60/291,476 (PTP). In certain embodiments the protein tyrosine phosphatase substrate comprises phosphorylated poly-(4:1)-Glu-Tyr, which in certain further embodiments comprises $^{32}P$. In certain embodiments the detectably labeled protein tyrosine phosphatase substrate comprises a reporter molecule that is a fluorophore, a radionuclide, a chemiluminescent agent, an enzyme, an immunologically detectable epitope or a chromaphore. In certain further embodiments, the fluorophore is selected from fluorescein, rhodamine, Texas Red, AlexaFluor-594, AlexaFluor-488, Oregon Green, BODIPY-FL or Cy-5.

According to certain embodiments of the present invention, the protein tyrosine phosphatase substrate comprises a polypeptide sequence derived from a protein selected from a PDGF receptor, VCP, $p130^{cas}$, EGF receptor, p210 bcr:abl, MAP

kinase, Shc, insulin receptor, lck, T cell receptor zeta chain, lysozyme, or reduced and carboxyamidomethylated and maleylated lysozyme (RCML). In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is an alkylating agent. In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog or N-ethylmaleimide. In certain embodiments the cell is a mammalian cell, which in certain embodiments is derived from a cell line and in certain further embodiments is derived from Rat-1 fibroblasts, COS cells, CHO cells or HEK-293 cells. In certain embodiments the step of isolating the protein tyrosine phosphatase comprises cell lysis, and in certain further embodiments the step of isolating comprises gel electrophoresis of the protein tyrosine phosphatase, and in certain further embodiments this step comprises electrophoresis of the protein tyrosine phosphatase in a gel comprising the detectably labeled protein tyrosine phosphatase substrate. In certain embodiments the method further comprises detecting the protein tyrosine phosphatase with an antibody that specifically binds to the phosphatase.

In certain embodiments of the present invention the stimulus increases reactive oxygen species in the sample, and in certain further embodiments the stimulus is a cytokine, a growth factor, a hormone, a cell stressor or a peptide. In certain embodiments the cell stressor is ROS or ultraviolet light. In certain embodiments the stimulus is PDGF, EGF, bFGF, insulin, GM-CSF, TGF-β1, IL-1, IL-3, IFN-γ, TNF-α, PHA, AT-2, thrombin, thyrotropin, parathyroid hormone, LPA, sphingosine-1-phosphate, serotonin, endothelin, acetylcholine, platelet activating factor, bradykinin or G-CSF.

In certain embodiments of the present invention there is provided a method for identifying a protein tyrosine phosphatase that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine with a biological sample comprising a cell

that comprises at least one protein tyrosine phosphatase; isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly modified by a PTP active site-binding agent in a cell. In certain embodiments, the invention provides a method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine with a biological sample comprising a cell that comprises SHP-2; isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a SHP-2 active site invariant cysteine, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly modified by a PTP active site-binding agent in a cell. In another embodiment, the invention provides a method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine with a biological sample comprising a cell that comprises PTP1B; isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group

of a PTP1B active site invariant cysteine, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly modified by a PTP active site-binding agent in a cell. In another embodiment, the invention provides a method for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine with a biological sample comprising a cell that comprises TC45; isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a TC45 active site invariant cysteine, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly modified by a PTP active site-binding agent in a cell.

In certain further embodiments, the step of isolating is performed anaerobically. In certain embodiments the PTP active site-binding agent is an agent that covalently binds to the PTP active site or an agent that non-covalently binds to the PTP active site. In certain embodiments the PTP active site-binding agent is a sulfonated compound or a vanadate compound. In certain embodiments the PTP active site-binding agent covalently and reversibly modifies a sulfhydryl group of a PTP active site invariant cysteine. In certain further embodiments the step of determining comprises reversing a covalent modification of a sulfhydryl group of a PTP active site invariant cysteine. In certain still further embodiments the step of reversing comprises contacting the PTP with a reducing agent. In certain still further embodiments the reducing agent is dithiothreitol, dithioerythritol or 2-mercaptoethanol. In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a

sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog or N-ethylmaleimide.

According to certain other embodiments of the present invention, there is provided a method for identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect protein tyrosine phosphatase active site invariant cysteine from modification; isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the protein tyrosine phosphatase active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell. In a certain embodiment, the invention provides a method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a SHP-2 active site invariant cysteine from modification; isolating the SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the SHP-2 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one

of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is a reversibly modified component of an inducible biological signaling pathway in a cell. In another embodiment, that which is provided is a method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises PTP1B with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a PTP1B active site invariant cysteine from modification; isolating the PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the PTP1B active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is a reversibly modified component of an inducible biological signaling pathway in a cell. In a certain embodiment, the invention provides a method for identifying a TC45 protein tyrosine phosphatase (TC45) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises TC45 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a TC45 active site invariant cysteine from modification; isolating the TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the TC45 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is

present, and therefrom identifying a TC45 that is a reversibly modified component of an inducible biological signaling pathway in a cell.

In certain embodiments the step of isolating is performed anaerobically. In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog or N-ethylmaleimide.

In certain other embodiments the invention provides a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a protein tyrosine phosphatase that is reversibly oxidized in a first biological sample comprising a cell that comprises at least one PTP according to the above described method steps of contacting, isolating and determining; (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises the PTP that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of the PTP; (c) isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway. In certain embodiments the step of isolating in the method recited in (a) is performed

anaerobically, and in certain embodiments the step of isolating recited in (c) is performed anaerobically.

In a certain embodiment, the invention provides a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell according to a method comprising (i) contacting a first biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2 in the cell; (ii)isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; (iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell; (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises SHP-2 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2; (c) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

In another embodiment of the invention is provided a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell according to a method comprising (i) contacting a first biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell; (ii) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; (iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell; (b)contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises PTP1B that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B; (c) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

The invention also provides a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a TC45 protein

tyrosine phosphatase (TC45) that is reversibly oxidized in a cell according to a method comprising (i) contacting a first biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45 in the cell; (ii) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; (iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell; (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises TC45 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45; (c) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a TC45 active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

These and other aspects of the present invention will become evident upon reference to the following detailed description and attached drawings. In addition, various references are set forth herein which describe in more detail certain aspects of this invention, and are therefore incorporated by reference in their entireties.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic for use of the "in-gel" phosphatase assay to identify PTPs that are susceptible to stimulus-induced oxidation.

Figure 2 shows reversible oxidation of multiple PTPs concomitant with tyrosine phosphorylation in Rat-1 cells treated with $H_2O_2$. Figure 2A illustrates an in-gel PTP assay. Serum-deprived Rat-1 cells were exposed to various concentrations of $H_2O_2$ for 1 min, harvested, and lysed in the absence (lane 1) or presence (lanes 2-7) of 10 mM iodoacetic acid (IAA). Figure 2B presents an immunoblot of tyrosine phosphorylated proteins immunoprecipitated from lysates of $H_2O_2$-treated cells with Ab PT-66, then immunoblotted with anti-pTyr Ab (G104). Figure 2C presents an in-gel PTP assay. After pre-incubation of Rat-1 cells in the absence or presence of 30 mM NAC, the cells were exposed to 200 μM $H_2O_2$ and lysed in the presence of 10 mM IAA at the indicated times. Figure 2D shows an in-gel PTP assay of oxidized PTPs. Rat-1 cells were serum-starved in the absence or presence of 2.5 mM BSO for 16 h. $H_2O_2$ (200 μM) was added for 2 minutes, then removed by washing the cells with fresh culture media. Incubation was continued until the cells were harvested in lysis buffer containing 10 mM IAA at the times indicated. Arrows indicate PTPs for which reduction/reactivation displayed dependence on intracellular GSH.

Figure 3 illustrates that $H_2O_2$-induced mitogenic signaling was associated with inactivation of PTPs. Figure 3A presents an in-gel PTP assay. Purified SHP-2 (E76A mutant, 1 ng/lane) was incubated with PBS, $H_2O_2$, or t-BHP at 37 °C for 5 minutes. Aliquots were then incubated at room temperature for an additional 5 minutes, either in the absence (- IAA) or presence (+IAA) of 4 mM IAA. Figure 3B shows images of ROS-induced DCF fluorescence in Rat-1 cells pre-loaded with 20 μM $H_2$DCFDA in the dark and then exposed to $H_2O_2$ or t-BHP (each at 200 μM). The cells are shown at magnification 400X (upper panels). Cells ($1 \times 10^5$) that underwent the same treatment as above were harvested and resuspended in Hanks' solution, then immediately subjected to flow cytometric analysis to measure ROS-induced DCF fluorescence (lower panels). The basal peak indicates background fluorescence, whereas the rightward shifted peak indicates ROS-induced DCF fluorescence. Figure

3C depicts an in-gel PTP assay of oxidized PTPs. Cells were exposed to $H_2O_2$ and t-BHP (each at 200 μM) for the indicated times and lysed in the presence of 10 mM IAA. Figure 3D presents an immunoblot of cell lysates prepared from cells exposed to $H_2O_2$ and t-BHP (each at 200 μM). Tyrosine phosphorylated proteins were immunoprecipitated with Ab PT-66, followed by immunoblotting with anti-pTyr Ab G104 (upper panel). An aliquot of lysate from each treatment was immunoblotted with anti-phospho-MAPK Ab and subsequently with anti-MAPK Ab (lower panel).

Figure 4 shows PDGF induced oxidation of a 70k PTP in Rat-1 cells. Figure 4A represents an in-gel PTP assay. Serum-starved Rat-1 cells were exposed to 50 ng/ml PDGF-BB for the times indicated. Lysates were prepared in the presence of 10 mM IAA and subjected to in-gel PTP assay. The arrow indicates a 70 kDa PTP that was transiently oxidized following stimulation of Rat-1 cells with PDGF. The result shown is representative of four independent experiments. Figure 4B: Cells were pre-incubated in the absence or presence of 30 mM NAC for 40 minutes. Excess NAC was removed prior to addition of PDGF (50 ng/ml). PDGF-induced oxidation of the 70 kDa PTP, which was impaired in the presence of NAC (arrow), was visualized by the modified in-gel PTP assay. Figure 4C: Cells were treated with NAC and PDGF as described above. PDGFR was immunoprecipitated from lysates with Ab-X and immunoblotted with anti-pTyr Ab G104. The same filter was subsequently re-probed with Ab-X (upper panels). Aliquots of cell lysate from each treatment were immunoblotted with anti-phosho-MAPK Ab and re-probed with anti-MAPK Ab (lower panels).

Figure 5 illustrates identification of the 70kDa PTP that was susceptible to PDGF-induced oxidation as SHP-2. Figure 5A: Serum-starved Rat-1 cells were exposed to PDGF (50 ng/ml) for the indicated times. The PDGFR and associated proteins were immunoprecipitated with antibody Ab-X, and pTyr proteins were visualized by immunoblotting with anti-pTyr Ab G104 (upper panel). The same filter was re-probed with anti-PDGFR, anti-SHP-2, anti-GAP, and anti-p85 PI3K Abs. The positions of PDGFR (solid arrow) and SHP-2 (open arrow) are indicated. Figure 5B: Rat-1 cells, either untreated (-) or stimulated with 50 ng/ml PDGF (+), were harvested in lysis buffer containing 10 mM IAA. Lysates were incubated with antibody specific

for either SHP-2 or SHP-1 and subjected to an in-gel PTP assay (upper panel). The arrow denotes the position of the 70 kDa PTP that was inactivated in response to PDGF and immunodepleted from cell lysates with antibodies to SHP-2. The lower panel illustrates an immunoblot to show the immunodepletion of SHP-2.

Figure 6 demonstrates oxidation and inactivation of SHP-2 that was induced by PDGF but not by EGF or FGF. Figure 6A: Rat-1 cells were incubated with 20 μM CM-$H_2$DCFDA in the dark for 20 minutes, then exposed to peptide growth factors (50 ng/ml) for an additional 10 mins. Images of ROS-induced DCF fluorescence are shown at 50X magnification. The data are representative of four independent experiments. Figure 6B presents an in-gel PTP assay of oxidized PTPs. Cells were exposed to peptide growth factors for the indicated times and lysed in the presence of 10 mM IAA. Figure 6C illustrates an immunoblot of cell lysates from each treatment group immunoblotted with anti-phosho-MAPK Ab (upper panel). The immunoblot was reprobed with anti-MAPK Ab (lower panel).

Figure 7 shows that the pool of PDGFR-associated SHP-2, which was oxidized and inactivated in response to PDGF, was also involved in down-regulation of MAPK signaling. Rat-1 cells were transiently transfected with plasmids expressing WT or Y1009F mutant G-CSFR/PDGFR chimeric receptor, or with a plasmid encoding Green Fluorescence Protein (GFP) as a control for expression. Figure 7A: After exposure to 100 ng/ml G-CSF for 5 min, the chimeric receptors were immunoprecipiated from lysates with antibody Ab-X and immunoblotted with anti-pTyr Ab G104. Immunoprecipitation of the receptors was verified by immunoblotting with Ab-X. The same filter was stripped and reprobed with anti-SHP-2 Ab. Expression of the chimeric receptors was verified by immunoblotting an aliquot of each lysate with Ab-X, which recognizes the intracellular segment of the PDGFR, and subsequently with anti-G-CSFR Ab, which recognizes the extracellular segment of chimeric receptors. Figure 7B presents an in-gel PTP assay of Rat-1 cell lysates. Transfected Rat-1 cells were treated with G-CSF for the indicated times and then lysed in the presence of 10 mM IAA. The arrow denotes the position of SHP-2. Figure 7C: The wild-type and mutant chimeric receptors were immunoprecipitated at the indicated times and immunoblotted with anti-pTyr Ab (G104) (top panel). The same filter was

re-probed with anti-PDGFR Ab-X (bottom panel). Figure 7D presents an immunoblot of cell lysates from each treatment blotted with anti-phosho-MAPK Ab (upper panel), and then re-probed with anti-MAPK Ab (lower panel). Figure 7E presents a densitometric analysis of the gel image, which illustrates the ratio of phosphorylated MAPK (upper panel of 7D) over total MAPK (lower panel of 7D).

Figure 8 presents a listing of PTPs.

Figure 9 illustrates an in-gel PTP assay that shows protection from IAA-inactivation of PTP activity in PHA-stimulated peripheral blood mononuclear lymphocytes pre-treated with a PTP active site-binding agent.

Figure 10 illustrates that hydrogen peroxide is a mediator of insulin signaling. Figure 10A presents images of ROS-induced DCF fluorescence by fluorescence microscopy (50x magnification) of serum-starved Rat-1 cells exposed to 50 nM insulin. The data are representative of three independent experiments. Figure 10B: Rat-1 cells were transiently transfected with different quantities of plasmid encoding human catalase. Two days after transfection, cells were serum-deprived and then stimulated with 50 nM insulin (INS) for 10 min. The cells were lysed, and catalase expression was verified by immunoblotting with anti-catalase antibody (top panel). The insulin receptor β (IR-β) subunit was immunoprecipitated from 400 μg of lysate with antibody 29B4. Immunoblotting was performed with anti-$pYpY^{1162/1163}$, and subsequently with anti-IR-β antibody clone C-19 as a loading control (middle panel). An aliquot of lysate (30 μg) was subjected to immunoblotting with anti-phospho-PKB/AKT antibody. The same filter was then stripped and reprobed with anti-PKB/AKT antibody as a loading control (bottom panel).

Figure 11 shows that insulin induced the transient oxidation of PTP1B and TC45. For each experiment, serum-starved Rat-1 cells were exposed to 50 nM insulin for the indicated times. Lysates were prepared under anaerobic conditions in the presence of 10 mM IAA and then subjected to in-gel PTP assays. Figure 11A: The arrowheads indicate that 50 kDa and 45 kDa PTPs were transiently oxidized in response to insulin. Figure B and Figure C present in-gel PTP assays. Total lysate (400 μg) was immunoprecipitated with normal IgG (labeled C), anti-PTP1B antibody (FG6), or anti-TC45 antibody (1910H) coupled to protein G-Sepharose beads. After

immunoprecipitation, the immune complexes and supernatants were subjected to in-gel PTP assays. Figure 11B shows immunodepletion of the 50 kDa PTP from the lysate with anti-PTP1B antibody. Figure 11C illustrates immunodepletion of the 45 kDa PTP with antibody specific for TC45. The lane marked "Lys" represents cell lysate prior to immunodepletion. The lower panels illustrate immunoblots of total lysate and the supernatants following immunodepletion, using either anti-PTP1B antibody (Figure 11B, lower panels) or anti-TC45 antibody (Figure 11C, lower panels). The same blots were subsequently reprobed with anti-SHP-2 antibody to ensure loading of equal amounts of protein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method of identifying any PTP that has been reversibly modified (*e.g.*, oxidized, or reversibly modified by a PTP active site-binding agent) in a cellular context (*i.e.*, within a cell, or *in vivo*), and in particular to any modification of a PTP active site invariant cysteine residue that can be reversed with a reducing agent. As described herein, typically such modification/ oxidation of a PTP is accompanied by transient inactivation of the enzyme. Described herein is the unexpected discovery that reversible oxidation of a PTP in a cellular context renders such a PTP resistant to irreversible inactivation of the enzyme by a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP active site invariant cysteine. This discovery is exploited to provide the invention method in a manner whereby one or more PTPs of interest may be non-specifically isolated from a cell—the invention method thus does not require any specific preparation and/or purification of a particular PTP that may be suspected of undergoing reversible modification/ oxidation *in vivo*, such as recombinant cloning and expression of the PTP (which would require a polynucleotide encoding each PTP of interest) or immunoprecipitation of the PTP (which would require an antibody specific for each PTP of interest). Instead, the method may be practiced using a cell that comprises one or a plurality of PTPs, where the method permits determination of one or more reversibly modified/ oxidized PTPs in a cell even where the identities of the particular PTPs that are expressed in the cell are not known *a priori*.

Accordingly, the one or more PTPs in a cell that are transiently modified/ oxidized at the time the cell is contacted with the sulfhydryl-reactive agent that is capable of irreversibly (*e.g.*, covalently) modifying a sulfhydryl group of a PTP active site invariant cysteine are not inactivated by the sulfhydryl-reactive agent, and such PTPs can subsequently be detected on the basis of their ability to catalytically dephosphorylate a PTP substrate after reversal (*e.g.*, under reducing conditions) of the transient modification/ oxidation event. Hence, and according to non-limiting theory, contact with a stimulus may induce a biological signaling pathway in a cell, which pathway comprises at least one PTP (and potentially a plurality of PTPs) that is reversibly modified at invariant cysteine (*e.g.*, oxidized to form sulfenic acid) in response to the stimulus, and which is therefore reversibly protected from irreversible modification of its active site invariant cysteine during subsequent isolation of the PTP in the presence of a sulfhydryl-reactive agent (*e.g.*, iodoacetamide) that is capable of so modifying the invariant cysteine. By way of contrast, any PTPs that are not reversibly and protectively modified in the course of the cellular response to the stimulus will be susceptible to permanent inactivation by the sulfhydryl agent during the PTP isolation procedure. Isolated PTPs are then exposed to conditions that reverse the reversible protection from modification of the PTP active site invariant cysteine (*e.g.*, reducing conditions), such that PTP enzyme activity is restored only to those PTPs that have undergone the reversible protective modification. This activity can then be determined as a level of dephosphorylation of a detectably labeled PTP substrate as described herein. While this non-limiting theoretical model of the PTP modifications that may or may not occur in the course of practicing the subject invention method pertains to reversible oxidation of PTP active site invariant cysteine in response to a stimulus, as described herein the invention is not intended to be so limited, and also contemplates any other reversible modification to a PTP (*e.g.*, by transient occupancy of the PTP active site by a PTP active site-binding agent that is capable of reversibly modifying a PTP active site invariant cysteine) that can be reversed, for example, a modification that is reversed by a reducing agent.

In certain embodiments the invention thus also provides a method for identifying a PTP that is a reversibly oxidized component of an inducible biological

signaling pathway that is induced by a stimulus which may trigger reversible modification, for example, oxidation, of one or more PTPs. In such embodiments, any stimulus that is known to be, or suspected of being, capable of inducing a biological signaling pathway is contacted with a cell comprising one or a plurality of PTPs, and recoverable PTP catalytic activity is assessed following inactivation of unmodified (*e.g.*, non-oxidized) PTPs with a sulfhydryl-reactive agent that is capable of irreversibly (*e.g.*, covalently) modifying a sulfhydryl group of a PTP active site invariant cysteine. In certain related embodiments, prior to the step of contacting the cell with a stimulus, the cell may be contacted with a PTP active site-binding agent, to determine whether such a PTP active site-binding agent alters (*i.e.*, increases or decreases in a statistically significant manner) the level of substrate dephosphorylation by one or more PTPs present in the cell, where PTPs that have retained the ability to dephosphorylate substrate have been reversibly and protectively modified (*e.g.*, oxidized) as a result of the biological signaling pathway induced by the stimulus. Non-limiting examples of PTP active site-binding agents for use in such embodiments include PTP inhibitors as disclosed in Zhang et al. (2002 *Ann. Rev. Pharmacol. Toxicol.* 42:209-234), Iverson et al. (2001 *Biochemistry* 40:14812-20) and Jia et al. (2001 *J. Med. Chem.* 44:4584). Certain such agents may be sulfonated compounds or vanadate compounds (*e.g.*, sodium orthovanadate); these and other PTP active site-binding agents are known to the art and/or may be identified according to established methodologies, including those described herein and in the cited references.

As described in greater detail below, in certain preferred embodiments determination of PTP substrate dephosphorylation, by one or more reversibly oxidized PTPs isolated anaerobically from a cell in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP active site invariant cysteine on any unmodified PTP, is accomplished using a modified "in-gel" PTP activity assay to allow visualization of a profile of PTPs that are reversibly oxidized following a particular stimulus. Anaerobic isolation conditions may be employed for one or more PTPs identified according to the present method, and whether and/or to what extent such conditions may be needed will vary with each PTP, as well as with the nature of the reversible modification (*i.e.*, oxidative *vs.* non-oxidative) experienced by

the PTP in a cell. Typically, anaerobic isolation of one or more PTPs relates to performing procedures for isolation of PTPs from a sample in an environment that is substantially reduced in its exposure to or content of oxygen gas, for instance, by conducting the isolation in an enclosure in which ambient air has been substantially replaced by an inert gas such as argon or nitrogen. Other procedures for creating an anaerobic atmosphere for PTP isolation may also be employed and will be familiar to those skilled in the art in view of the present disclosure, which describes examples of oxidative modification of PTPs that are detected following anaerobic isolation of the PTP.

Exemplary results using the modified "in-gel" PTP activity assay provided herein indicated that several PTPs could be identified that were oxidized and inactivated reversibly in Rat-1 cells following stimulation with $H_2O_2$, and that this event was important for peroxide-induced mitogenic signaling. Examples provided below show that platelet-derived growth factor (PDGF) stimulation of Rat-1 cells induced the oxidation and inhibition of the SH2 domain-containing PTP known as SHP-2 (*see* Hof et al., 1998 *Cell* 92:441-50), which facilitated mitogenic signaling in these cells in response to the growth factor. Additional examples provided show that insulin-induced signaling resulted in the oxidation and inhibition of two PTPs, PTP1B and the 45 kDa spliced variant of TC-PTP, TC45 (*see* Mosinger et al., 1992 *Proc. Natl. Acad. Sci. USA* 89:499-503; Tiganis et al., 1998 *Mol. Cell Biol.* 18:1622-34; Tiganis et al., 1999 *J. Biol. Chem.* 274:27768-75). The invention contemplates extending these analyses to identify and characterize other PTPs and their roles in the control of a broad array of biological signal transduction pathways.

Certain preferred embodiments of the invention therefore relate to a method wherein stimulus-induced oxidation within a cellular context (*i.e., in vivo*) provides a means of "tagging" (*e.g.,* reversibly protecting from a sulfhydryl-reactive agent) those PTPs that are integral to the regulation of the cellular signal transduction pathways initiated by that stimulus. Alkylation with a sulfhydryl-reactive agent that is capable of covalently, and preferably irreversibly, modifying a sulfhydryl group of a PTP active site invariant cysteine, for example, iodoacetamide (IAA), can be used to inactivate and thereby functionally subtract out the bulk of the PTPs, which being

unaffected by the stimulus and hence not transiently oxidized, are unprotected from the sulfhydryl reagent. Following reduction to reverse the transient oxidation and return the transiently inactivated PTP to an active state, the stimulus-responsive (*i.e.*, oxidatively protected) PTPs can be isolated and identified on the basis of phosphatase activity, demonstrable as dephosphorylation of a PTP substrate using any of a variety of well established procedures as provided herein and as known to the art. (See, *e.g.*, Flint et al., 1993 *EMBO J. 12*:1937-1946; Tonks et al., 1991 *Meths. Enzymol.* 201:427-42; Tonks et al., 1988 *J. Biol. Chem.* 263:6722). Reducing conditions that are suitable for determining PTP substrate dephosphorylation by a catalytically competent phosphatase (*i.e.*, an "active" PTP) can be achieved using compositions and methods well known to the art in view of the present disclosure. The precise reducing conditions may vary as a function of the particular PTP for which activity following reversible inactivation is to be determined; common reducing agents for establishing such conditions include, by way of illustration and not limitation, dithiothreitol (Cleland's reagent), dithioerythritol and 2-mercaptoethanol (β-mercaptoethanol).

The "in-gel" phosphatase assay described herein comprises a modification of an existing technique (Burridge and Nelson, 1995 *Anal. Biochem. 232*, 56-64) and provides one such preferred procedure for demonstrating PTP activity toward (phosphorylated) PTP substrates as provided herein. The modified in-gel phosphatase assay features electrophoretic separation and renaturation, under reducing conditions, of a plurality of PTPs in a gel impregnated with a detectably labeled PTP substrate, but with regard to the step of determining dephosphorylation of a detectably labeled PTP substrate by a PTP according to the methods of disclosed herein, the invention is not intended to be so limited. For example some PTPs, in particular certain of the receptor-like forms, may not renature efficiently in the "in-gel" PTP activity assay (Burridge and Nelson, 1995). The invention therefore contemplates incorporation of any suitable method for determining a level of dephosphorylation of a detectably labeled PTP substrate by a PTP, which may vary according to the physicochemical properties (*e.g.*, conformational stability in a variety of chemical environments) of particular PTPs, and which can be selected by a person having ordinary skill in the art readily and without undue experimentation based on the instant disclosure.

For example, suitable phosphatase assays may include in-gel assays using non-denaturing gel systems. Additional methodologies for assaying PTP-mediated substrate dephosphorylation may include proteomics-based strategies, for example, using solid-phase immobilized, broad specificity PTP active site-directed inhibitors (such as phenylarsine oxide coupled to agarose) as affinity matrices for the purification and identification of oxidation-sensitive PTPs. As also noted above, other embodiments contemplate exposure of cells comprising an inducible biological signaling pathway to one or more PTP active site-binding agents (*e.g.*, Zhang et al. 2002 *Ann. Rev. Pharmacol. Toxicol.* 42:209-234; Iverson et al. 2001 *Biochemistry* 40:14812-20; Jia et al. 2001 *J. Med. Chem.* 44:4584) prior to contacting these cells with a stimulus that induces the signaling pathway. Recoverable activity may then be assayed in PTPs that are protectively modified, by reversible oxidation, when the PTPs are isolated in the presence of a sulfhydryl-reactive agent, wherein further the active site-binding agent may be employed to facilitate PTP isolation. By combining these approaches with the use of substrate-trapping mutant forms of the PTPs thus identified (*e.g.*, Flint et al., 1997 *Proc. Natl. Acad. Sci. USA* 94:1680-1685), the physiological substrate specificities of these enzymes can be determined to further characterize the components of biological signaling pathways that comprise PTPs. Additional characterization of biological signaling pathway components identified using the methods of the present invention may be achieved using specific binding proteins to detect such components. Preferred examples of such binding proteins include antibodies, receptors, counterreceptors, ligands, and the like, for example, an antibody that, as provided herein, specifically binds to a phosphatase, or an antibody that specifically binds to a phosphopeptide such as phosphotyrosine, phosphoserine or phosphothreonine.

PTPs

As used herein, a phosphatase is a member of the PTP family if it contains the signature motif [I/V]HCXAGXXR[S/T]G (SEQ ID NO:98). Dual specificity PTPs, *i.e.*, PTPs which dephosphorylate both phosphorylated tyrosine and phosphorylated serine or threonine, are also suitable for use in the invention.

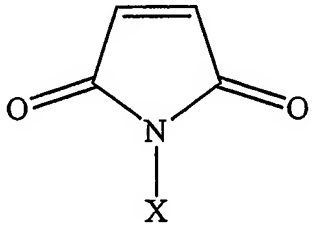
Appropriate PTPs for use in the present invention include any PTP family member, for example, any PTP described in Andersen et al. (2001 *Mol. Cell. Biol.* 21:7117) or shown in Figure 8, or any dual specificity phosphatase including but not limited to PYST-1, MKP-1, MKP-2, MKP-4, MKP-5, MKP-7, hVH5, PAC1, VHR, or any dual specificity phosphatase disclosed in WO00/65069 (DSP-5), WO00/65068 (DSP-10), WO00/63393 (DSP-8), WO00/60100 (DSP-9), WO00/60099 (DSP-4), WO00/60098 (DSP-7), WO00/60092 (DSP-3), WO00/56899 (DSP-2), WO00/53636 (DSP-1), WO00/09656 (MKP), AU5475399 (MKP), AU8479498, WO99/02704, WO97/06245 (MKP), WO01/83723, WO01/57221, WO01/05983, WO01/02582, WO01/02581, U.S.A.N. 09/955,732 (DSP-15), U.S.A.N. 09/964,277 (DSP-16), U.S.A.N. 60/268,837 (DSP-17) or U.S.A.N. 60/291,476 (PTP) and in certain preferred embodiments including, but not limited to, PTP1B (*e.g.*, GenBank Accession Nos. M31724 (SEQ ID NOS: 1-2); NM_002827 (SEQ ID NOS: 3-4); NM_011201 (SEQ ID NOS: 5-6); M31724 (SEQ ID NOS: 7-8); M33689 (SEQ ID NOS: 9-10); M33962 (SEQ ID NOS: 11-12)), PTP-PEST (*e.g.*, GenBank Accession Nos. D13380 (SEQ ID NOS: 68-69); M93425 (SEQ ID NOS: 70-71); S69184 (SEQ ID NOS: 72-73); X86781 (SEQ ID NOS: 74-75); D38072 (SEQ ID NOS: 76-77)), PTPγ, LAR, MKP-1, CRYPα, PTPcryp2, DEP-1 (*e.g.*, GenBank Accession Nos. U10886 (SEQ ID NOS: 41-42); D37781 (SEQ ID NOS: 43-44); AAB26475 (SEQ ID NO: 45); D45212 (SEQ ID NOS: 46-47); U40790 (SEQ ID NOS: 48-49)), SAP1, PCPTP1, PTPSL, STEP, HePTP, PTPIA2, PTPNP, PTPNE6, PTPμ, PTPX1, PTPX10, SHP-1 (*e.g.*, GenBank Accession Nos. M74903 (SEQ ID NOS: 86-87); X62055 (SEQ ID NOS: 88-89); M77273 (SEQ ID NOS: 90-91); X82817 (SEQ ID NO: 92); X82818 (SEQ ID NO: 93); M90388 (SEQ ID NOS: 94-95); U77038 (SEQ ID NOS: 96-97)), SHP-2 (*e.g.*, GenBank Accession Nos. D13540 (SEQ ID NOS: 25-26); L03535 (SEQ ID NOS: 27-28); L07527 (SEQ ID NOS: 29-30); X70766 (SEQ ID NOS: 31-32); L08807 (SEQ ID NO: 33); S78088 (SEQ ID NOS: 34-35); S39383 (SEQ ID NO: 36); D84372 (SEQ ID NOS: 13-14); U09307 (SEQ ID NOS: 15-16)), PTPBEM1, PTPBEM2, PTPBYP, PTPesp, PTPoc, PTP-PEZ, PTP-MEG1, MEG2, LC-PTP, TC-PTP (*e.g.*, GenBank Accession Nos. M25393 (SEQ ID NOS: 17-18); M81478 (SEQ ID NO: 19); M80737 (SEQ ID NO: 20); M81477 (SEQ ID NOS: 21-22); X58828 (SEQ ID NOS: 23-24); NM_002828 (SEQ ID NOS:

___ and ___), TC45 (*e.g.*, NM_080422 (SEQ ID NOS: ___ and ___)), CD45 (*e.g.*, GenBank Accession Nos. Y00638 (SEQ ID NOS: 78-79); Y00062 (SEQ ID NOS: 80-81); M92933 (SEQ ID NOS: 82-83); M10072 (SEQ ID NOS: 84-85); LAR, cdc14 (which includes cdc14a (*e.g.*, GenBank Accession Nos. AF122013 (SEQ ID NOS: 50-51); AF064102 (SEQ ID NOS: 52-53); AF064103 (SEQ ID NOS: 54-55); Li et al., 1997 *J. Biol. Chem.* 272:29403; U.S. Patent No. 6,331,614) and cdc14b (*e.g.*, GenBank Accession Nos. AF064104 (SEQ ID NOS: 56-57); AF064105 (SEQ ID NOS: 58-59); AF023158 (SEQ ID NOS: 60-61); Li et al., 1997 *J. Biol. Chem.* 272:29403), RPTP-α, RPTP-ε, RKPTP, LyPTP, PEP, BDP1, PTP20, PTPK1, PTPS31, PTPGMC, GLEPP1, OSTPTP, PTPtep, PTPRL10, PTP2E, PTPD1, PTPD2, PTP36, PTPBAS, PTPBL, BTPBA14, PTPTyp, HDPTP, PTPTD14, PTPα, PTPβ, PTPδ, PTPε (*e.g.*, GenBank Accession Nos. X54134 (SEQ ID NOS: 62-63); D83484 (SEQ ID NOS: 64-65); D78610 (SEQ ID NOS: 66-67)), PTPκ, PTPλ, PTPμ, PTPρ, PTPψ, PTPϕ, PTPζ, PTPNU3 and PTPH1 (*e.g.*, GenBank Accesion Nos. M64572 (SEQ ID NOS: 37-38) and S39392 (SEQ ID NOS: 39-40)), and mutated forms thereof.

As noted above, and particularly with regard to the identification and selection of suitable PTP substrates as provided herein, including peptide fragments having sequences derived from portions of polypeptides identified as physiological PTP substrates, the present invention relates in part to the use of substrate trapping mutant protein tyrosine phosphatases (PTPs) derived from a PTP that has been mutated in a manner that does not cause significant alteration of the Michaelis-Menten constant (Km) of the enzyme, but which results in a reduction of the catalytic rate constant (Kcat). In certain embodiments, the PTP catalytic domain invariant aspartate residue may be replaced with another amino acid. In certain other embodiments, the substrate trapping mutant PTP may be mutated by replacement of a catalytic domain cysteine residue. Under certain conditions *in vivo*, a PTP enzyme may itself undergo tyrosine phosphorylation in a manner that can alter interactions between the PTP and other molecules, including PTP substrates. Thus, in certain embodiments the substrate trapping mutant PTP may be further mutated by replacement of at least one tyrosine residue with an amino acid that is not capable of being phosphorylated. Substrate trapping mutant PTPs are disclosed, for example, in U.S. Patent Nos. 5,912,138 and

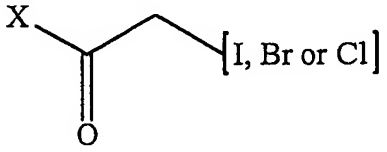
5,951,979 and in U.S. Application No. 09/334,575. Disclosure relating to the preparation and use of substrate trapping mutant PTPs, including PTPs having at least one tyrosine residue replaced with an amino acid that is not capable of being phosphorylated, and including identification of physiological PTP substrates, can be found in WO 00/75339.

According to particularly preferred embodiments of the methods of the present invention, PTPs in which the wildtype catalytic domain invariant cysteine residues are present, may be inactivated by sulfhydryl-reactive agents according to assay methods as disclosed herein. Preferably, such agents are sulfhydryl-reactive agents that are capable of covalently and irreversibly modifying a sulfhydryl group of a PTP active site invariant cysteine, for example alkylating agents such as N-ethylmaleimide (NEM), iodoacetamide (IAA) or iodoacetic acid. Other sulfhydryl-reactive agents that are capable of covalently modifying a sulfhydryl group of a PTP active site invariant cysteine include arsenic oxide; 4-vinyl pyridine and analogs and derivatives thereof; maleimide analogs conforming to the following structural formula:




wherein X is the remainder of the molecule, including linkers;

or halo-acetamido analogs conforming to the following structural formula:




wherein X is the remainder of the molecule, including linkers.

Useful sulfhydryl-reactive agents may also include other cysteine-reactive compounds, *i.e.*, chemically reactive species that covalently modify cysteine and/or adjacent residues, further including such compounds which do so stoichiometrically and without selectivity for PTP proteins or polypeptides.

The term "isolated" means that the material is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally occurring nucleic acid or polypeptide present in a living animal is not isolated, but the same nucleic acid or polypeptide, separated from some or all of the co-existing materials in the natural system, is isolated. Such nucleic acid could be part of a vector and/or such nucleic acid or polypeptide could be part of a composition (*e.g.*, a cell lysate), and still be isolated in that such vector or composition is not part of the natural environment for the nucleic acid or polypeptide. The term "gene" means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region "leader and trailer" as well as intervening sequences (introns) between individual coding segments (exons).

SAMPLES

According to the present invention, there is provided a method of identifying a protein tyrosine phosphatase that has been reversibly oxidized, typically in a biological sample. A "sample" as used herein refers to a biological sample containing at least one protein tyrosine phosphatase, and may be provided by obtaining a blood sample, biopsy specimen, tissue explant, organ culture or any other tissue or cell preparation from a subject or a biological source. A sample may further refer to a tissue or cell preparation in which the morphological integrity or physical state has been disrupted, for example, by dissection, dissociation, solubilization, fractionation, homogenization, biochemical or chemical extraction, pulverization, lyophilization, sonication or any other means for processing a sample derived from a subject or biological source. In certain preferred embodiments, the sample is a cell that comprises at least one PTP, and in certain particularly preferred embodiments the cell comprises an inducible biological signaling pathway, at least one component of which is a PTP.

In particularly preferred embodiments the cell is a mammalian cell, for example, Rat-1 fibroblasts, COS cells, CHO cells, HEK-293 cells or other well known model cell lines, which are available from the American Type Culture Collection (ATCC, Manassas, VA).

The subject or biological source may be a human or non-human animal, a primary cell culture or culture adapted cell line including but not limited to genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, immortalized or immortalizable cell lines, somatic cell hybrid cell lines, differentiated or differentiatable cell lines, transformed cell lines and the like. Optionally, in certain situations it may be desirable to treat cells in a biological sample with hydrogen peroxide and/or with another agent that directly or indirectly promotes reactive oxygen species (ROS) generation, including biological stimuli as described herein; in certain other situations it may be desirable to treat cells in a biological sample with a ROS scavenger, such as N-acetyl cysteine (NAC) or superoxide dismutase (SOD) or other ROS scavengers known in the art; in other situations cellular glutathione (GSH) may be depleted by treating cells with L-buthionine-SR-sulfoximine (Bso); and in other circumstances cells may be treated with pervanadate to enrich the sample in tyrosine phosphorylated proteins. Other means may also be employed to effect an increase in the population of tyrosine phosphorylated proteins present in the sample, including the use of a subject or biological source that is a cell line that has been transfected with at least one gene encoding a protein tyrosine kinase.

Additionally or alternatively, a biological signaling pathway may be induced in subject or biological source cells by contacting such cells with an appropriate stimulus, which may vary depending upon the signaling pathway under investigation, whether known or unknown. For example, a signaling pathway that, when induced, results in protein tyrosine phosphorylation and/or protein tyrosine dephosphorylation may be stimulated in subject or biological source cells using any one or more of a variety of well known methods and compositions known in the art to stimulate protein tyrosine kinase and/or PTP activity. These stimuli may include, without limitation, exposure of cells to cytokines, growth factors, hormones, peptides,

small molecule mediators, cell stressors (*e.g.*, ultraviolet light; temperature shifts; osmotic shock; ROS or a source thereof, such as hydrogen peroxide, superoxide, ozone, etc. or any agent that induces or promotes ROS production (see, *e.g.*, Halliwell and Gutteridge, *Free Radicals in Biology and Medicine* (3rd Ed.) 1999 Oxford University Press, Oxford, UK); heavy metals; alcohol) or other agents that induce PTK-mediated protein tyrosine phosphorylation and/or PTP-mediated phosphoprotein tyrosine dephosphorylation. Such agents may include, for example, interleukins (*e.g.*, IL-1, IL-3), interferons (*e.g.*, IFN-γ), human growth hormone, insulin, epidermal growth factor (EGF), platelet derived growth factor (PDGF), granulocyte colony stimulating factor (G-CSF), granulocyte-megakaryocyte colony stimulating factor (GM-CSF), transforming growth factor (*e.g.*, TGF-β1), tumor necrosis factor (*e.g.*, TNF-α) and fibroblast growth factor (FGF; *e.g.*, basic FGF (bFGF)), any agent or combination of agents capable of triggering T lymphocyte activation via the T cell receptor for antigen (TCR; TCR-inducing agents may include superantigens, specifically recognized antigens and/or MHC-derived peptides, MHC peptide tetramers (*e.g.*, Altman et al., 1996 *Science* 274:94-96) TCR-specific antibodies or fragments or derivatives thereof), lectins (*e.g.*, PHA, PWM, ConA, etc.), mitogens, G-protein coupled receptor agonists such as angiotensin-2, thrombin, thyrotropin, parathyroid hormone, lysophosphatidic acid (LPA), sphingosine-1-phosphate, serotonin, endothelin, acetylcholine, platelet activating factor (PAF) or bradykinin, as well as other agents with which those having ordinary skill in the art will be familiar (*see, e.g.*, Rhee et al., 10 October 2000 *Science's stke*, <http:www.stke.org/cgl/content/full/OC_sigtrans;2000/53/pel, and references cited therein; *see also* Gross et al., 1999 *J. Biol. Chem.* 274:26378-86; Prenzel et al., 1999 *Nature* .402:884-88; Ushio-Fukai et al., 1999 *J. Biol. Chem.* 274:22699-704; Holland et al., 1998 *Endothelium* 6:113-21; Daub et al., 1997 *EMBO J.* 16:7032-44; Krypianou et al., 1997 *Prostate* 32:266-71; Marumo et al., 1997 *Circulation* 96:2361-67).

As noted above, regulated tyrosine phosphorylation contributes to specific pathways for biological signal transduction, including those associated with cell division, cell survival, apoptosis, proliferation and differentiation, and "inducible signaling pathways" in the context of the present invention include transient or stable

associations or interactions among molecular components involved in the control of these and similar processes in cells. Depending on the particular pathway of interest, an appropriate parameter for determining induction of such pathway may be selected. For example, for signaling pathways associated with cell proliferation, there is available a variety of well known methodologies for quantifying proliferation, including, for example, incorporation of tritiated thymidine into cellular DNA, monitoring of detectable (*e.g.*, fluorimetric or colorimetric) indicators of cellular respiratory activity, or cell counting, or the like. Similarly, in the cell biology arts there are known multiple techniques for assessing cell survival (*e.g.*, vital dyes, metabolic indicators, etc.) and for determining apoptosis (*e.g.*, annexin V binding, DNA fragmentation assays, caspase activation, etc.). Other signaling pathways will be associated with particular cellular phenotypes, for example specific induction of gene expression (*e.g.*, detectable as transcription or translation products, or by bioassays of such products, or as nuclear localization of cytoplasmic factors), altered (*e.g.*, statistically significant increases or decreases) levels of intracellular mediators (*e.g.*, activated kinases or phosphatases, altered levels of cyclic nucleotides or of physiologically active ionic species, etc.), or altered cellular morphology, and the like, such that cellular responsiveness to a particular stimulus as provided herein can be readily identified to determine whether a particular cell comprises an inducible signaling pathway.

For example, a biological signaling pathway may be induced in a cell by a stimulus that induces or promotes ROS production. Cells may be stimulated with any one or more of a number of stimuli as provided herein, including those provided above, such as a cytokine, a growth factor (*e.g.*, PDGF), a hormone such as a polypeptide hormone (*e.g.*, insulin), a cell stressor, or a peptide. Intracellular production of ROS, including hydrogen peroxide, may be determined according to established methodologies using direct or indirect ROS indicators, for example, by using fluorescent ROS indicators such as 2',7'-dichlorofluorescein diacetate ($H_2$DCFDA) or 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate (CM-$H_2$DCFDA). ROS-induced DCF fluorescence can then be measured, for instance, by fluorimetry, fluorescence microscopy or flow cytofluorimetry, or according to other methods known in the art. ROS may also be detected in biological systems by any of a variety of other

techniques, including spin trapping, in which a reactive radical is allowed to react with a molecular trap to produce a long-lived radical, and also including molecular fingerprinting, which measures end-products of oxidative damage. Specific compositions and methods for such trapping, as well as other means for determining ROS, are known to the art and selection of a technique for identifying ROS may depend upon the particular reactive oxygen species that is to be detected (*see, e.g.,* Halliwell and Gutteridge, *supra*).

The effect of ROS production on phosphorylation and/or dephosphorylation of one or more polypeptide components of a signaling pathway may be examined by determining the level of phosphorylation of components in the particular pathway. For example, treatment of Rat-1 cells with PDGF, which has been shown to induce ROS production in various cell types (Bae et al., 2000, *supra*; Sundaresan et al. *supra*), results in a rapid increase in the tyrosine phosphorylation of cellular proteins and enhanced phosphorylation of MAPKs (*see also* Bazenet et al., 1996 *Mol. Cell Biol.* 16:6926-36; Klinghoffer et al., 2001 *Mol. Cell* 78:343-54; Yu et al., 2000 *J. Biol. Chem.* 275:19076-82). As another example, the effect of ROS production in the signal transduction pathway induced by insulin may be evaluated by determining the level of tyrosine phosphorylation of insulin receptor beta (IR-β) and/or of the downstream signaling molecule PKB/Akt and/or of any other downstream polypeptide that may be a component of a particular signal transduction pathway as provided herein.

A number of methods are described herein and known in the art for detection of one or more particular signal transduction pathway component polypeptides, and for determination of whether such polypeptides may be tyrosine-phosphorylated in cells following stimulation as described herein. Also described herein are methods for detecting such polypeptides, including determination of altered (*i.e.*, increased or decreased with statistical significance) tyrosine phosphorylation that may further include determination of the phosphorylation state of particular tyrosine residues at specified positions within a polypeptide sequence, which altered tyrosine phosphorylation may in certain embodiments be accompanied by the presence or absence of ROS production in the cells from which such polypeptides are obtained

(*e.g.*, as a result of exposure to a stimulus). Non-limiting examples of such detection methods include the use of reagents that specifically bind to signaling pathway components, for example, by immunological methods (*e.g.*, immunoprecipitation, immunoblotting, ELISA, radioimmunoprecipitation, and the like) that employ antibodies as provided herein that are capable of specifically binding a particular signaling pathway component polypeptide or a particular tyrosine-phosphorylated polypeptide. Additionally and as described in greater detail herein, in certain embodiments cellular ROS production induced by a stimulus may be partially or completely impaired, abrogated, inhibited or otherwise counteracted by inclusion of a ROS-neutralizing agent, for instance, by the presence of enzymes such as catalase ($H_2O_2$:$H_2O_2$ oxidoreductase) or superoxide dismutase (SOD; superoxide:superoxide oxidoreductase), or of free-radical scavengers or other agents known to the art that are capable of neutralizing the effects of ROS (*see, e.g.*, Halliwell and Gutteridge, *supra*).

SUBSTRATES

In preferred embodiments, a PTP substrate may be any naturally or non-naturally occurring phosphorylated peptide, polypeptide or protein that can specifically bind to and/or be dephosphorylated by a PTP (including dual specificity phosphatases) as provided herein, or any other phosphorylated molecule that can be a substrate of a PTP family member as provided herein. Non-limiting examples of known PTP substrates include the proteins VCP (see, *e.g.*, Zhang et al., 1999 *J. Biol. Chem.* 274:17806, and references cited therein), $p130^{cas}$, EGF receptor, p210 bcr:abl, MAP kinase, Shc (Tiganis et al., 1998 *Mol. Cell. Biol.* 18:1622-1634), insulin receptor, lck (lymphocyte specific protein tyrosine kinase, Marth et al., 1985 *Cell* 43:393), T cell receptor zeta chain, and phosphatidylinositol 3,4,5-triphosphate (Maehama et al., 1998 *J. Biol. Chem.* 273:13375).

As another example, tyrosine phosphorylated peptides identified with mutant PTPs from peptide libraries by the methods of Songyang et al. (1995 *Nature* *373*:536-539; 1993 *Cell* *72*:767-778) can be used herein in place of the complete tyrosine phosphorylated protein in PTP binding and/or catalytic assays. Optionally,

candidate peptide sequences may be selected and optimized for dephosphorylation or binding activity as described herein using other techniques such as affinity selection followed by mass spectrometric detection (*e.g.,* Pellegrini et al., 1998 *Biochemistry* 37:15598; Huyer et al., 1998 *Anal. Biochem.* 258:19) or by "inverse alanine scanning" (*e.g.,* Vetter et al., 2000 *J. Biol. Chem.* 275:2265). In certain particularly preferred embodiments, a PTP substrate is a tyrosine phosphorylated peptide, which may include a partial amino acid sequence, portion, region, fragment, variant, derivative or the like from a naturally or non-naturally tyrosine-phosphorylated peptide, polypeptide or protein that can specifically bind to and/or be dephosphorylated by a PTP. In preferred embodiments, the PTP substrate is detectably labeled as provided herein, such that it can be detectably dephosphorylated by a PTP family member, as also provided herein. A PTP substrate that is a tyrosine phosphorylated peptide typically comprises 2-700 amino acids. Preferred substrates as described herein include a random amino acid copolymer of poly-Glu-Tyr wherein the Glu:Tyr ratio is approximately 4:1; preparations of this copolymer may be polydisperse with respect to molecular mass and in certain preferred embodiments may have an average molecular mass of approximately 55-65 kDa. Other preferred substrates include reduced and carboxyamidomethylated and maleylated lysozyme (RCML, Flint et al., 1993 *EMBO J. 12*:1937-1946). In certain other embodiments, a PTP substrate may comprise a phosphotyrosine residue having an attached fluorescent label.

Identification and selection of PTP substrates as provided herein, for use in the present invention, may be performed according to procedures with which those having ordinary skill in the art will be familiar, or may, for example, be conducted according to the disclosures of WO 00/75339 or U.S. Application Number 09/334,575 and references cited therein. The phosphorylated protein/PTP complex may be isolated, for example, by conventional isolation techniques as described in U.S. Patent No. 5,352,660, including salting out, chromatography, electrophoresis, gel filtration, fractionation, absorption, polyacrylamide gel electrophoresis, agglutination, combinations thereof or other strategies. PTP substrates that are known may also be prepared according to well known procedures that employ principles of molecular biology and/or peptide synthesis (*e.g.,* Ausubel et al., 1993 *Current Protocols in*

*Molecular Biology*, Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., Boston, MA; Sambrook et al., 1989 *Molecular Cloning*, Second Ed., Cold Spring Harbor Laboratory, Plainview, NY; Fox, 1995 *Molec. Biotechnol.* 3:249; Maeji et al., 1995 *Pept. Res.* 8:33).

The PTP substrate peptides of the present invention may therefore be derived from PTP substrate proteins, polypeptides and peptides as provided herein having amino acid sequences that are identical or similar to tyrosine phosphorylated PTP substrate sequences known in the art. For example by way of illustration and not limitation, peptide sequences derived from the known PTP substrate proteins referred to above are contemplated for use according to the instant invention, as are peptides having at least 70% similarity (preferably 70% identity), more preferably 90% similarity (more preferably 90% identity) and still more preferably 95% similarity (still more preferably 95% identity) to the polypeptides described in references cited herein and in the Examples and to portions of such polypeptides as disclosed herein. As known in the art "similarity" between two polypeptides is determined by comparing the amino acid sequence and conserved amino acid substitutes thereto of the polypeptide to the sequence of a second polypeptide (*e.g.*, using GENEWORKS, Align or the BLAST algorithm, or another algorithm, as described above).

Thus, according to the present invention, substrates may include full length tyrosine phosphorylated proteins and polypeptides as well as fragments (*e.g.*, portions), derivatives or analogs thereof that can be phosphorylated at a tyrosine residue. Such fragments, derivatives and analogs include any PTP substrate polypeptide that retains at least the biological function of interacting with a PTP as provided herein, for example by forming a complex with a PTP and/or, in certain embodiments, undergoing PTP-catalyzed dephosphorylation. A fragment, derivative or analog of a peptide, protein or polypeptide as provided herein, including a PTP substrate polypeptide, and further including PTP substrates that are fusion proteins, may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue), and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the substrate polypeptide is fused with another

compound, such as a compound to increase the half-life of the polypeptide (*e.g.*, polyethylene glycol) or a detectable moiety such as a reporter molecule, or (iv) one in which additional amino acids are fused to the substrate polypeptide, including amino acids that are employed for purification of the substrate polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art.

Certain preferred substrates include phosphoproteins and phosphopeptide sequences that may be tyrosine phosphorylated and/or serine/threonine phosphorylated, for example, as may provide suitable phosphophorylated substrates for dual specificity phosphatases, which are described above. Examples of physiological substrates which may provide phosphoprotein or phosphopeptides sequences for use as PTP substrates, including fragments, variants and derivatives as provided herein, include PDGF receptor, VCP, $p130^{cas}$, EGF receptor, p210 bcr:abl, MAP kinase, Shc, insulin receptor, lck, and T cell receptor zeta chain. A number of non-physiological phosphoproteins and phosphopeptides are also known to be suitable PTP substrates, as described, for example, by Tonks et al. (1991 *Meths. Enzymol.* 201:427-42; 1988 *J. Biol. Chem.* 263:6722); these include, as non-limiting examples, poly-[Glu-Tyr], MBP and reduced and carboxyamidomethylated and maleylated lysozyme (RCML, Flint et al., 1993 *EMBO J. 12*:1937-1946).

In preferred embodiments the PTP substrate is detectably labeled, and in particularly preferred embodiments the PTP substrate is capable of generating a radioactive or a fluorescent signal. The PTP substrate can be detectably labeled by covalently or non-covalently attaching a suitable reporter molecule or moiety, for example a radionuclide such as $^{32}P$ (*e.g.*, Pestka et al., 1999 *Protein Expr. Purif.* 17:203-14), a radiohalogen such as iodine [$^{125}I$ or $^{131}I$] (*e.g.*, Wilbur, 1992 *Bioconjug. Chem.* 3:433-70), or tritium [$^{3}H$]; an enzyme; or any of various luminescent (*e.g.*, chemiluminescent) or fluorescent materials (*e.g.*, a fluorophore) selected according to the particular fluorescence detection technique to be employed, as known in the art and based upon the present disclosure. Fluorescent reporter moieties and methods for labeling PTP substrates as provided herein can be found, for example in Haugland (1996 *Handbook of Fluorescent Probes and Research Chemicals- Sixth Ed.*, Molecular

Probes, Eugene, OR; 1999 *Handbook of Fluorescent Probes and Research Chemicals-Seventh Ed.*, Molecular Probes, Eugene, OR, http://www.probes.com/lit/) and in references cited therein. Particularly preferred for use as such a fluorophore in the subject invention methods are fluorescein, rhodamine, Texas Red, AlexaFluor-594, AlexaFluor-488, Oregon Green, BODIPY-FL, umbelliferone, dichlorotriazinylamine fluorescein, dansyl chloride, phycoerythrin or Cy-5. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, biotin, alkaline phosphatase, β-galactosidase and acetylcholinesterase. Appropriate luminescent materials include luminol, and suitable radioactive materials include radioactive phosphorus [$^{32}P$].

ANTIBODIES

Also contemplated by the present invention is the use according to certain embodiments of an antibody that specifically binds to a PTP, which may include peptides, polypeptides, and other non-peptide molecules that specifically bind to a PTP. As used herein, a molecule is said to "specifically bind" to a PTP if it reacts at a detectable level with the PTP, but does not react detectably with peptides containing an unrelated sequence, or a sequence of a different phosphatase. Preferred binding molecules include antibodies, which may be, for example, polyclonal, monoclonal, single chain, chimeric, anti-idiotypic, or CDR-grafted immunoglobulins, or fragments thereof, such as proteolytically generated or recombinantly produced immunoglobulin $F(ab')_2$, Fab, Fv, and Fd fragments. Binding properties of an antibody to a PTP may generally be assessed using immunodetection methods including, for example, an enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, immunoblotting and the like, which may be readily performed by those having ordinary skill in the art. In certain preferred embodiments, the invention method may comprise isolating one or more particular PTPs with an antibody that specifically binds to each phosphatase; such embodiments may include without limitation methodologies for immuno-isolation (*e.g.*, immunoprecipitation, immunoaffinity chromatography) and/or immunodetection (*e.g.*, western blot) of at least one PTP.

Methods well known in the art may be used to generate antibodies, polyclonal antisera or monoclonal antibodies that are specific for a PTP; a number of

PTP-specific antibodies are also commercially available. Antibodies also may be produced as genetically engineered immunoglobulins (Ig) or Ig fragments designed to have desirable properties. For example, by way of illustration and not limitation, antibodies may include a recombinant IgG that is a chimeric fusion protein having at least one variable (V) region domain from a first mammalian species and at least one constant region domain from a second, distinct mammalian species. Most commonly, a chimeric antibody has murine variable region sequences and human constant region sequences. Such a murine/human chimeric immunoglobulin may be "humanized" by grafting the complementarity determining regions (CDRs) derived from a murine antibody, which confer binding specificity for an antigen, into human-derived V region framework regions and human-derived constant regions. Fragments of these molecules may be generated by proteolytic digestion, or optionally, by proteolytic digestion followed by mild reduction of disulfide bonds and alkylation. Alternatively, such fragments may also be generated by recombinant genetic engineering techniques.

As used herein, an antibody is said to be "immunospecific" or to "specifically bind" a PTP polypeptide if it reacts at a detectable level with PTP, preferably with an affinity constant, $K_a$, of greater than or equal to about $10^4$ $M^{-1}$, more preferably of greater than or equal to about $10^5$ $M^{-1}$, more preferably of greater than or equal to about $10^6$ $M^{-1}$, and still more preferably of greater than or equal to about $10^7$ $M^{-1}$. Affinities of binding partners or antibodies can be readily determined using conventional techniques, for example, those described by Scatchard et al. (*Ann. N.Y. Acad. Sci. USA 51*:660 (1949)) and by surface plasmon resonance (SPR; BIAcore™, Biosensor, Piscataway, NJ). For surface plasmon resonance, target molecules are immobilized on a solid phase and exposed to ligands in a mobile phase running along a flow cell. If ligand binding to the immobilized target occurs, the local refractive index changes, leading to a change in SPR angle, which can be monitored in real time by detecting changes in the intensity of the reflected light. The rates of change of the surface plasmon resonance signal can be analyzed to yield apparent rate constants for the association and dissociation phases of the binding reaction. The ratio of these values gives the apparent equilibrium constant (affinity). *See, e.g.,* Wolff et al., *Cancer Res. 53*:2560-2565 (1993).

Antibodies may generally be prepared by any of a variety of techniques known to those having ordinary skill in the art. *See, e.g.,* Harlow et al., *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory (1988). In one such technique, an animal is immunized with PTP as an antigen to generate polyclonal antisera. Suitable animals include, for example, rabbits, sheep, goats, pigs, cattle, and may also include smaller mammalian species, such as mice, rats, and hamsters, or other species.

An immunogen may be comprised of cells expressing PTP, purified or partially purified PTP polypeptides or variants or fragments (*e.g.*, peptides) thereof, or PTP peptides. PTP peptides may be generated by proteolytic cleavage or may be chemically synthesized. For instance, nucleic acid sequences encoding PTP polypeptides are provided herein, such that those skilled in the art may routinely prepare these polypeptides for use as immunogens. Polypeptides or peptides useful for immunization may also be selected by analyzing the primary, secondary, and tertiary structure of PTP according to methods known to those skilled in the art, in order to determine amino acid sequences more likely to generate an antigenic response in a host animal. *See, e.g.*, Novotny, 1991 *Mol. Immunol. 28*:201-207; Berzofsky, 1985 *Science* 229:932-40.

Preparation of the immunogen for injection into animals may include covalent coupling of the PTP polypeptide (or variant or fragment thereof), to another immunogenic protein, for example, a carrier protein such as keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA). In addition, the PTP peptide, polypeptide, or PTP-expressing cells to be used as immunogen may be emulsified in an adjuvant. *See, e.g.*, Harlow et al., *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory (1988). In general, after the first injection, animals receive one or more booster immunizations according to a preferred schedule that may vary according to, *inter alia*, the antigen, the adjuvant (if any) and/or the particular animal species. The immune response may be monitored by periodically bleeding the animal, separating the sera out of the collected blood, and analyzing the sera in an immunoassay, such as an ELISA or Ouchterlony diffusion assay, or the like, to determine the specific antibody titer. Once an antibody titer is established, the animals may be bled periodically to accumulate the polyclonal antisera. Polyclonal antibodies that bind specifically to the PTP polypeptide

or peptide may then be purified from such antisera, for example, by affinity chromatography using protein A, or the PTP polypeptide, immobilized on a suitable solid support.

Monoclonal antibodies that specifically bind to PTP polypeptides or fragments or variants thereof, and hybridomas, which are immortal eukaryotic cell lines, that produce monoclonal antibodies having the desired binding specificity, may also be prepared, for example, using the technique of Kohler and Milstein (*Nature*, *256*:495-497; 1976, *Eur. J. Immunol.* *6*:511-519 (1975)) and improvements thereto. An animal—for example, a rat, hamster, or preferably mouse—is immunized with a PTP immunogen prepared as described above. Lymphoid cells that include antibody-forming cells, typically spleen cells, are obtained from an immunized animal and may be immortalized by fusion with a drug-sensitized myeloma (*e.g.*, plasmacytoma) cell fusion partner, preferably one that is syngeneic with the immunized animal and that optionally has other desirable properties (*e.g.*, inability to express endogenous Ig gene products). The lymphoid (*e.g.*, spleen) cells and the myeloma cells may be combined for a few minutes with a membrane fusion-promoting agent, such as polyethylene glycol or a nonionic detergent, and then plated at low density on a selective medium that supports the growth of hybridoma cells, but not unfused myeloma cells. A preferred selection media is HAT (hypoxanthine, aminopterin, thymidine). After a sufficient time, usually about one to two weeks, colonies of cells are observed. Single colonies are isolated, and antibodies produced by the cells may be tested for binding activity to the PTP polypeptide, or variant or fragment thereof. Hybridomas producing monoclonal antibodies with high affinity and specificity for a PTP antigen are preferred. Hybridomas that produce monoclonal antibodies that specifically bind to a PTP polypeptide or variant or fragment thereof are therefore contemplated by the present invention.

Monoclonal antibodies may be isolated from the supernatants of hybridoma cultures. An alternative method for production of a murine monoclonal antibody is to inject the hybridoma cells into the peritoneal cavity of a syngeneic mouse, for example, a mouse that has been treated (*e.g.*, pristane-primed) to promote formation of ascites fluid containing the monoclonal antibody. Contaminants may be

removed from the subsequently (usually within 1-3 weeks) harvested ascites fluid by conventional techniques, such as chromatography, gel filtration, precipitation, extraction, or the like. For example, antibodies may be purified by affinity chromatography using an appropriate ligand selected based on particular properties of the monoclonal antibody (*e.g.*, heavy or light chain isotype, binding specificity, etc.). Examples of a suitable ligand, immobilized on a solid support, include Protein A, Protein G, an anti-constant region (light chain or heavy chain) antibody, an anti-idiotype antibody and a PTP polypeptide or fragment or variant thereof.

Human monoclonal antibodies may be generated by any number of techniques with which those having ordinary skill in the art will be familiar. Such methods include but are not limited to, Epstein Barr Virus (EBV) transformation of human peripheral blood cells (*e.g.*, containing B lymphocytes), *in vitro* immunization of human B cells, fusion of spleen cells from immunized transgenic mice carrying human immunoglobulin genes inserted by yeast artificial chromosomes (YAC), isolation from human immunoglobulin V region phage libraries, or other procedures as known in the art and based on the disclosure herein.

For example, one method for generating human monoclonal antibodies includes immortalizing human peripheral blood cells by EBV transformation. *See, e.g.*, U.S. Patent No. 4,464,456. An immortalized cell line producing a monoclonal antibody that specifically binds to a PTP polypeptide (or a variant or fragment thereof) can be identified by immunodetection methods as provided herein, for example, an ELISA, and then isolated by standard cloning techniques. Another method to generate human monoclonal antibodies, *in vitro* immunization, includes priming human splenic B cells with antigen, followed by fusion of primed B cells with a heterohybrid fusion partner. *See, e.g.*, Boerner et al., 1991 *J. Immunol. 147*:86-95.

Still another method for the generation of human PTP-specific monoclonal antibodies and polyclonal antisera for use in the present invention relates to transgenic mice. *See, e.g.*, U.S. Patent No. 5,877,397; Bruggemann et al., 1997 *Curr. Opin. Biotechnol. 8*:455-58; Jakobovits et al., 1995 *Ann. N. Y. Acad. Sci. 764*:525-35. In these mice, human immunoglobulin heavy and light chain genes have been artificially introduced by genetic engineering in germline configuration, and the

endogenous murine immunoglobulin genes have been inactivated. *See, e.g.*, Bruggemann et al., 1997 *Curr. Opin. Biotechnol. 8*:455-58. For example, human immunoglobulin transgenes may be mini-gene constructs, or transloci on yeast artificial chromosomes, which undergo B cell-specific DNA rearrangement and hypermutation in the mouse lymphoid tissue. *See*, Bruggemann et al., 1997 *Curr. Opin. Biotechnol. 8*:455-58. Human monoclonal antibodies specifically binding to PTP may be obtained by immunizing the transgenic animals, fusing spleen cells with myeloma cells, selecting and then cloning cells producing antibody, as described above. Polyclonal sera containing human antibodies may also be obtained from the blood of the immunized animals.

Chimeric antibodies, specific for a PTP, including humanized antibodies, may also be generated according to the present invention. A chimeric antibody has at least one constant region domain derived from a first mammalian species and at least one variable region domain derived from a second, distinct mammalian species. *See, e.g.*, Morrison et al., 1984, *Proc. Natl. Acad. Sci. USA*, *81*:6851-55. In preferred embodiments, a chimeric antibody may be constructed by cloning the polynucleotide sequence that encodes at least one variable region domain derived from a non-human monoclonal antibody, such as the variable region derived from a murine, rat, or hamster monoclonal antibody, into a vector containing a nucleic acid sequence that encodes at least one human constant region. *See, e.g.*, Shin et al., 1989 *Methods Enzymol. 178*:459-76; Walls et al., 1993 *Nucleic Acids Res. 21*:2921-29. By way of example, the polynucleotide sequence encoding the light chain variable region of a murine monoclonal antibody may be inserted into a vector containing a nucleic acid sequence encoding the human kappa light chain constant region sequence. In a separate vector, the polynucleotide sequence encoding the heavy chain variable region of the monoclonal antibody may be cloned in frame with sequences encoding the human IgG1 constant region. The particular human constant region selected may depend upon the effector functions desired for the particular antibody (*e.g.*, complement fixing, binding to a particular Fc receptor, etc.). Another method known in the art for generating chimeric antibodies is homologous recombination (*e.g.*, U.S. Patent No. 5,482,856).

Preferably, the vectors will be transfected into eukaryotic cells for stable expression of the chimeric antibody.

A non-human/human chimeric antibody may be further genetically engineered to create a "humanized" antibody. Such a humanized antibody may comprise a plurality of CDRs derived from an immunoglobulin of a non-human mammalian species, at least one human variable framework region, and at least one human immunoglobulin constant region. Humanization may in certain embodiments provide an antibody that has decreased binding affinity for a PTP when compared, for example, with either a non-human monoclonal antibody from which a PTP binding variable region is obtained, or a chimeric antibody having such a V region and at least one human C region, as described above. Useful strategies for designing humanized antibodies may therefore include, for example by way of illustration and not limitation, identification of human variable framework regions that are most homologous to the non-human framework regions of the chimeric antibody. Without wishing to be bound by theory, such a strategy may increase the likelihood that the humanized antibody will retain specific binding affinity for a PTP, which in some preferred embodiments may be substantially the same affinity for a PTP polypeptide or variant or fragment thereof, and in certain other preferred embodiments may be a greater affinity for PTP. *See, e.g.*, Jones et al., 1986 *Nature 321*:522-25; Riechmann et al., 1988 *Nature 332*:323-27. Designing such a humanized antibody may therefore include determining CDR loop conformations and structural determinants of the non-human variable regions, for example, by computer modeling, and then comparing the CDR loops and determinants to known human CDR loop structures and determinants. *See, e.g.*, Padlan et al., 1995 *FASEB 9*:133-39; Chothia et al., 1989 *Nature*, *342*:377-383. Computer modeling may also be used to compare human structural templates selected by sequence homology with the non-human variable regions. *See, e.g.*, Bajorath et al., 1995 *Ther. Immunol. 2*:95-103; EP-0578515-A3. If humanization of the non-human CDRs results in a decrease in binding affinity, computer modeling may aid in identifying specific amino acid residues that could be changed by site-directed or other mutagenesis techniques to partially, completely or supra-optimally (*i.e.*, increase to a level greater than that of the non-humanized antibody) restore affinity. Those having ordinary skill in the art are

familiar with these techniques, and will readily appreciate numerous variations and modifications to such design strategies.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments or $F(ab')_2$ fragments, which may be prepared by proteolytic digestion with papain or pepsin, respectively. The antigen binding fragments may be separated from the Fc fragments by affinity chromatography, for example, using immobilized protein A or protein G, or immobilized PTP polypeptide, or a suitable variant or fragment thereof. Those having ordinary skill in the art can routinely and without undue experimentation determine what is a suitable variant or fragment based on characterization of affinity purified antibodies obtained, for example, using immunodetection methods as provided herein. An alternative method to generate Fab fragments includes mild reduction of $F(ab')_2$ fragments followed by alkylation. *See, e.g.,* Weir, *Handbook of Experimental Immunology*, 1986, Blackwell Scientific, Boston.

According to certain embodiments, non-human, human, or humanized heavy chain and light chain variable regions of any of the above described Ig molecules may be constructed as single chain Fv (sFv) polypeptide fragments (single chain antibodies). *See, e.g.*, Bird et al., 1988 *Science 242*:423-426; Huston et al., 1988 *Proc. Natl. Acad. Sci. USA 85*:5879-5883. Multi-functional sFv fusion proteins may be generated by linking a polynucleotide sequence encoding an sFv polypeptide in-frame with at least one polynucleotide sequence encoding any of a variety of known effector proteins. These methods are known in the art, and are disclosed, for example, in EP-B1-0318554, U.S. Patent No. 5,132,405, U.S. Patent No. 5,091,513, and U.S. Patent No. 5,476,786. By way of example, effector proteins may include immunoglobulin constant region sequences. *See, e.g.*, Hollenbaugh et al., 1995 *J. Immunol. Methods 188*:1-7. Other examples of effector proteins are enzymes. As a non-limiting example, such an enzyme may provide a biological activity for therapeutic purposes (*see, e.g.,* Siemers et al., 1997 *Bioconjug. Chem. 8*:510-19), or may provide a detectable activity, such as horseradish peroxidase-catalyzed conversion of any of a number of well-known substrates into a detectable product, for diagnostic uses. Still other examples of sFv fusion proteins include Ig-toxin fusions, or immunotoxins, wherein the sFv polypeptide

is linked to a toxin. Those having ordinary skill in the art will appreciate that a wide variety of polypeptide sequences have been identified that, under appropriate conditions, are toxic to cells. As used herein, a toxin polypeptide for inclusion in an immunoglobulin-toxin fusion protein may be any polypeptide capable of being introduced to a cell in a manner that compromises cell survival, for example, by directly interfering with a vital function or by inducing apoptosis. Toxins thus may include, for example, ribosome-inactivating proteins, such as *Pseudomonas aeruginosa* exotoxin A, plant gelonin, bryodin from *Bryonia dioica*, or the like. *See, e.g.*, Thrush et al., 1996 *Annu. Rev. Immunol. 14*:49-71; Frankel et al., 1996 *Cancer Res. 56*:926-32. Numerous other toxins, including chemotherapeutic agents, anti-mitotic agents, antibiotics, inducers of apoptosis (or "apoptogens", see, *e.g.*, Green and Reed, 1998, *Science 281*:1309-1312), or the like, are known to those familiar with the art, and the examples provided herein are intended to be illustrative without limiting the scope and spirit of the invention.

The sFv may, in certain embodiments, be fused to peptide or polypeptide domains that permit detection of specific binding between the fusion protein and antigen (*e.g.*, a PTP). For example, the fusion polypeptide domain may be an affinity tag polypeptide. Binding of the sFv fusion protein to a binding partner (*e.g.*, a PTP) may therefore be detected using an affinity polypeptide or peptide tag, such as an avidin, streptavidin or a His (*e.g.*, polyhistidine) tag, by any of a variety of techniques with which those skilled in the art will be familiar. Detection techniques may also include, for example, binding of an avidin or streptavidin fusion protein to biotin or to a biotin mimetic sequence (*see, e.g.*, Luo et al., 1998 *J. Biotechnol. 65*:225 and references cited therein), direct covalent modification of a fusion protein with a detectable moiety (*e.g.*, a labeling moiety), non-covalent binding of the fusion protein to a specific labeled reporter molecule, enzymatic modification of a detectable substrate by a fusion protein that includes a portion having enzyme activity, or immobilization (covalent or non-covalent) of the fusion protein on a solid-phase support.

The sFv fusion protein of the present invention, comprising a PTP-specific immunoglobulin-derived polypeptide fused to another polypeptide such as an effector peptide having desirable affinity properties, may therefore include, for

example, a fusion protein wherein the effector peptide is an enzyme such as glutathione-S-transferase. As another example, sFv fusion proteins may also comprise a PTP-specific Ig polypeptide fused to a *Staphylococcus aureus* protein A polypeptide; protein A encoding nucleic acids and their use in constructing fusion proteins having affinity for immunoglobulin constant regions are disclosed generally, for example, in U.S. Patent 5,100,788. Other useful affinity polypeptides for construction of sFv fusion proteins may include streptavidin fusion proteins, as disclosed, for example, in WO 89/03422; U.S. 5,489,528; U.S. 5,672,691; WO 93/24631; U.S. 5,168,049; U.S. 5,272,254 and elsewhere, and avidin fusion proteins (see, *e.g.,* EP 511,747). As provided herein, sFv polypeptide sequences may be fused to fusion polypeptide sequences, including effector protein sequences, that may include full length fusion polypeptides and that may alternatively contain variants or fragments thereof.

An additional method for selecting antibodies that specifically bind to a PTP polypeptide or variant or fragment thereof is by phage display. *See, e.g.*, Winter et al., 1994 *Annul. Rev. Immunol.* 12:433-55; Burton et al., 1994 *Adv. Immunol.* 57:191-280. Human or murine immunoglobulin variable region gene combinatorial libraries may be created in phage vectors that can be screened to select Ig fragments (Fab, Fv, sFv, or multimers thereof) that bind specifically to a PTP polypeptide or variant or fragment thereof. *See, e.g.*, U.S. Patent No. 5,223,409; Huse et al., 1989 *Science* 246:1275-81; Kang et al., 1991 *Proc. Natl. Acad. Sci. USA 88*:4363-66; Hoogenboom et al., 1992 *J. Molec. Biol. 227*:381-388; Schlebusch et al., 1997 *Hybridoma 16*:47-52 and references cited therein. For example, a library containing a plurality of polynucleotide sequences encoding Ig variable region fragments may be inserted into the genome of a filamentous bacteriophage, such as M13 or a variant thereof, in frame with the sequence encoding a phage coat protein, for instance, gene III or gene VIII of M13, to create an M13 fusion protein. A fusion protein may be a fusion of the coat protein with the light chain variable region domain and/or with the heavy chain variable region domain.

According to certain embodiments, immunoglobulin Fab fragments may also be displayed on the phage particle, as follows. Polynucleotide sequences encoding Ig constant region domains may be inserted into the phage genome in frame with a coat

protein. The phage coat fusion protein may thus be fused to an Ig light chain or heavy chain fragment (Fd). For example, from a human Ig library, the polynucleotide sequence encoding the human kappa constant region may be inserted into a vector in frame with the sequence encoding at least one of the phage coat proteins. Additionally or alternatively, the polynucleotide sequence encoding the human IgG1 CH1 domain may be inserted in frame with the sequence encoding at least one other of the phage coat proteins. A plurality of polynucleotide sequences encoding variable region domains (*e.g.*, derived from a DNA library) may then be inserted into the vector in frame with the constant region-coat protein fusions, for expression of Fab fragments fused to a bacteriophage coat protein.

Phage that display an Ig fragment (*e.g.*, an Ig V-region or Fab) that binds to a PTP polypeptide may be selected by mixing the phage library with PTP or a variant or a fragment thereof, or by contacting the phage library with a PTP polypeptide immobilized on a solid matrix under conditions and for a time sufficient to allow binding. Unbound phage are removed by a wash, which typically may be a buffer containing salt (*e.g.*, NaCl) at a low concentration, preferably with less than 100 mM NaCl, more preferably with less than 50 mM NaCl, most preferably with less than 10 mM NaCl, or, alternatively, a buffer containing no salt. Specifically bound phage are then eluted with an NaCl-containing buffer, for example, by increasing the salt concentration in a step-wise manner. Typically, phage that bind the PTP with higher affinity will require higher salt concentrations to be released. Eluted phage may be propagated in an appropriate bacterial host, and generally, successive rounds of PTP binding and elution can be repeated to increase the yield of phage expressing PTP-specific immunoglobulin. Combinatorial phage libraries may also be used for humanization of non-human variable regions. *See, e.g.,* Rosok et al., 1996 *J. Biol. Chem. 271*:22611-18; Rader et al., 1998 *Proc. Natl. Acad. Sci. USA 95*:8910-15. The DNA sequence of the inserted immunoglobulin gene in the phage so selected may be determined by standard techniques. *See,* Sambrook et al., 1989 *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press. The affinity selected Ig-encoding sequence may then be cloned into another suitable vector for expression of the Ig

fragment or, optionally, may be cloned into a vector containing Ig constant regions, for expression of whole immunoglobulin chains.

Phage display techniques may also be used to select polypeptides, peptides or single chain antibodies that bind to PTP. For examples of suitable vectors having multicloning sites into which candidate nucleic acid molecules (*e.g.*, DNA) encoding such peptides or antibodies may be inserted, *see, e.g.*, McLafferty et al., *Gene 128*:29-36, 1993; Scott et al., 1990 *Science 249*:386-390; Smith et al., 1993 *Methods Enzymol. 217*:228-257; Fisch et al., 1996, *Proc. Natl. Acad. Sci. USA* 93:7761-66. The inserted DNA molecules may comprise randomly generated sequences, or may encode variants of a known peptide or polypeptide domain that specifically binds to a PTP polypeptide, or variant or fragment thereof, as provided herein. Generally, the nucleic acid insert encodes a peptide of up to 60 amino acids, more preferably a peptide of 3 to 35 amino acids, and still more preferably a peptide of 6 to 20 amino acids. The peptide encoded by the inserted sequence is displayed on the surface of the bacteriophage. Phage expressing a binding domain for a PTP polypeptide may be selected on the basis of specific binding to an immobilized PTP polypeptide as described above. As provided herein, well-known recombinant genetic techniques may be used to construct fusion proteins containing the fragment thereof. For example, a polypeptide may be generated that comprises a tandem array of two or more similar or dissimilar affinity selected PTP binding peptide domains, in order to maximize binding affinity for PTP of the resulting product.

In certain other embodiments, the invention contemplates PTP-specific antibodies that are multimeric antibody fragments. Useful methodologies are described generally, for example in Hayden et al. 1997, *Curr Opin. Immunol. 9*:201-12; Coloma et al., 1997 *Nat. Biotechnol. 15*:159-63). For example, multimeric antibody fragments may be created by phage techniques to form miniantibodies (U.S. Patent No. 5,910 573) or diabodies (Holliger et al., 1997, *Cancer Immunol. Immunother. 45*:128-130). Multimeric fragments may be generated that are multimers of a PTP-specific Fv, or that are bispecific antibodies comprising a PTP-specific Fv noncovalently associated with a second Fv having a different antigen specificity. *See, e.g.*, Koelemij et al., 1999 *J. Immunother. 22*:514-24. As another example, a multimeric antibody may comprise a

bispecific antibody having two single chain antibodies or Fab fragments. According to certain related embodiments, a first Ig fragment may be specific for a first antigenic determinant on a PTP polypeptide (or variant or fragment thereof), while a second Ig fragment may be specific for a second antigenic determinant of the PTP polypeptide. Alternatively, in certain other related embodiments, a first immunoglobulin fragment may be specific for an antigenic determinant on a PTP polypeptide or variant or fragment thereof, and a second immunoglobulin fragment may be specific for an antigenic determinant on a second, distinct (*i.e.,* non-PTP) molecule. Also contemplated are bispecific antibodies that specifically bind PTP, wherein at least one antigen-binding domain is present as a fusion protein.

Introducing amino acid mutations into PTP-binding immunoglobulin molecules may be useful to increase the specificity or affinity for PTP, or to alter an effector function. Immunoglobulins with higher affinity for PTP may be generated by site-directed mutagenesis of particular residues. Computer assisted three-dimensional molecular modeling may be employed to identify the amino acid residues to be changed, in order to improve affinity for the PTP polypeptide . *See, e.g.*, Mountain et al., 1992, *Biotechnol. Genet. Eng. Rev.* 10: 1-142. Alternatively, combinatorial libraries of CDRs may be generated in M13 phage and screened for immunoglobulin fragments with improved affinity. *See, e.g.*, Glaser et al., 1992, *J. Immunol. 149*:3903-3913; Barbas et al., 1994 *Proc. Natl. Acad. Sci. USA 91*:3809-13; U.S. Patent No. 5,792, 456).

Effector functions may also be altered by site-directed mutagenesis. *See, e.g.*, Duncan et al., 1988 *Nature 332*:563-64; Morgan et al., 1995 *Immunology 86*:319-24; Eghtedarzedeh-Kondri et al., 1997 *Biotechniques 23*:830-34. For example, mutation of the glycosylation site on the Fc portion of the immunoglobulin may alter the ability of the immunoglobulin to fix complement. *See, e.g.,* Wright et al., 1997 *Trends Biotechnol. 15*:26-32. Other mutations in the constant region domains may alter the ability of the immunoglobulin to fix complement, or to effect antibody-dependent cellular cytotoxicity. *See, e.g.*, Duncan et al., 1988 *Nature 332*:563-64; Morgan et al., 1995 *Immunology 86*:319-24; Sensel et al., 1997 *Mol. Immunol. 34*:1019-29.

The nucleic acid molecules encoding an antibody or fragment thereof that specifically binds PTP, as described herein, may be propagated and expressed according to any of a variety of well-known procedures for nucleic acid excision, ligation, transformation and transfection. Thus, in certain embodiments expression of an antibody fragment may be preferred in a prokaryotic host, such as *Escherichia coli* (*see, e.g.,* Pluckthun et al., 1989 *Methods Enzymol. 178*:497-515). In certain other embodiments, expression of the antibody or a fragment thereof may be preferred in a eukaryotic host cell, including yeast (*e.g.*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Pichia pastoris*), animal cells (including mammalian cells) or plant cells. Examples of suitable animal cells include, but are not limited to, myeloma, COS, CHO, or hybridoma cells. Examples of plant cells include tobacco, corn, soybean, and rice cells. By methods known to those having ordinary skill in the art and based on the present disclosure, a nucleic acid vector may be designed for expressing foreign sequences in a particular host system, and then polynucleotide sequences encoding the PTP binding antibody (or fragment thereof) may be inserted. The regulatory elements will vary according to the particular host.

A PTP-binding immunoglobulin (or fragment thereof) as described herein may contain a detectable moiety or label such as an enzyme, cytotoxic agent or other reporter molecule, including a dye, radionuclide, luminescent group, fluorescent group, or biotin, or the like. The PTP-specific immunoglobulin or fragment thereof may be radiolabeled for diagnostic or therapeutic applications. Techniques for radiolabeling of antibodies are known in the art. *See, e.g.*, Adams 1998 *In Vivo* 12:11-21; Hiltunen 1993 *Acta Oncol. 32*:831-9. Therapeutic applications are described in greater detail below and may include use of the PTP-binding antibody (or fragment thereof) in conjunction with other therapeutic agents. The antibody or fragment may also be conjugated to a cytotoxic agent as known in the art and provided herein, for example, a toxin, such as a ribosome-inactivating protein, a chemotherapeutic agent, an anti-mitotic agent, an antibiotic or the like.

As provided herein and according to methodologies well known in the art, polyclonal and monoclonal antibodies may be used for the affinity isolation of PTP polypeptides. *See, e.g.,* Hermanson et al., *Immobilized Affinity Ligand Techniques*,

Academic Press, Inc. New York, 1992. Briefly, an antibody (or antigen-binding fragment thereof) may be immobilized on a solid support material, which is then contacted with a sample comprising the polypeptide of interest (*e.g.*, a PTP). Following separation from the remainder of the sample, the polypeptide is then released from the immobilized antibody.

METHODS FOR DETECTING PTP EXPRESSION

Certain embodiments of the present invention provide methods that employ antibodies raised against PTP for assay purposes. Certain assays involve using an antibody or other agent to detect the presence or absence of PTP, or proteolytic fragments thereof. Assays may generally be performed using any of a variety of samples obtained from a biological source, as provided herein.

To detect a PTP protein, the reagent is typically an antibody, as provided herein. There are a variety of assay formats known to those having ordinary skill in the art for using an antibody to detect a polypeptide in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. For example, the assay may be performed in a Western blot format, wherein a protein preparation from the biological sample is resolved by gel electrophoresis, transferred to a suitable membrane and allowed to react with the antibody. The presence of the antibody on the membrane may then be detected using a suitable detection reagent, as described below. In certain embodiments of the present invention, this format may be preferred to determine, establish or confirm the specific identity of a PTP that is identified as being reversibly modified or reversibly oxidized in a cell.

In another embodiment, isolation of a PTP may involve the use of antibody immobilized on a solid support to bind to the target PTP and remove it from the remainder of the sample. The bound PTP may then be detected using a second antibody or reagent that contains a reporter group. Alternatively, a competitive assay may be utilized, in which a PTP polypeptide is labeled with a reporter group and allowed to bind to the immobilized antibody after incubation of the antibody with the sample. The extent to which components of the sample inhibit the binding of the

labeled polypeptide to the antibody is indicative of the reactivity of the sample with the immobilized antibody, and as a result, indicative of the level of PTP in the sample.

The solid support may be any material known to those having ordinary skill in the art to which the antibody may be attached, such as a test well in a microtiter plate, a nitrocellulose filter or another suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic such as polystyrene or polyvinylchloride. The antibody may be immobilized on the solid support using a variety of techniques known to those in the art, which are amply described in the patent and scientific literature.

In certain embodiments, the assay for detection of PTP in a sample is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the biological sample, such that PTP within the sample is allowed to bind to the immobilized antibody (a 30 minute incubation time at room temperature is generally sufficient). Unbound sample is then removed from the immobilized PTP/antibody complexes and a second antibody (containing a reporter group such as an enzyme, dye, radionuclide, luminescent group, fluorescent group or biotin) capable of binding to a different site on the PTP is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products. Standards and standard additions may be used to determine the level of PTP in a sample, using well known techniques.

In a related aspect of the present invention, kits for detecting a reversibly modified PTP, and for determining PTP phosphatase activity, are provided. Such kits may be designed for detecting the level of PTP, or may detect phosphatase activity of

PTP in a direct phosphatase assay or a coupled phosphatase assay. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of a PTP typically contains a reagent that specifically binds to the PTP protein; the reagent is typically an antibody. Such kits also contain a reporter group suitable for direct or indirect detection of the reagent (*i.e.,* the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.,* horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those having ordinary skill in the art.

Kits for detecting PTP activity typically comprise a PTP substrate in combination with a suitable buffer. PTP activity may be specifically detected by performing an immunoprecipitation step with a PTP-specific antibody prior to performing a phosphatase assay as described above. Other reagents for use in detecting dephosphorylation of substrate may also be provided.

SCREENING ASSAYS FOR AGENTS

Where a PTP is identified that is a reversibly modified/ oxidized component of a biological signaling pathway as provided herein, by using the methods of the present invention, it is further contemplated that in certain further embodiments the invention provides a screening assay for an agent that alters an inducible biological signaling pathway. According to such assays, a cell comprising the PTP (and hence the inducible pathway wherein the PTP is reversibly modified) is contacted with a stimulus that induces the pathway in the absence and presence of a candidate agent, under conditions permissive for induction of the pathway by the stimulus. PTPs are then isolated from the cell in the presence of a sulfhydryl-reactive agent that is capable of covalently (*e.g.,* irreversibly) modifying a sulfhydryl group of the PTP active site invariant cysteine where, as described herein, the signaling pathway component PTP

that is reversibly modified (*e.g.*, oxidized) is protected from inactivation by such sulfhydryl agent, and PTP catalytic activity is determined by any of a variety of established methods, as also provided herein, after the reversibly modified PTP is reactivated by reversal of the modification (*e.g.*, under reducing conditions). Decreased substrate dephosphorylation when the pathway is induced in the presence of the candidate agent, relative to the level of dephosphorylation when induction transpires in the absence of the candidate agent, indicates that the agent is an inhibitor or antagonist (*e.g.*, results in PTP catalytic activity in the cell that is decreased in a statistically significant manner) of the reversibly modified PTP. Conversely, increased substrate dephosphorylation when the pathway is induced in the presence of the candidate agent, relative to the level of dephosphorylation when induction transpires in the absence of the candidate agent, indicates that the agent is a potentiator or agonist (*i.e.*, an activity enhancer) of the reversibly modified PTP (*e.g.*, results in PTP catalytic activity in the cell that is increased in a statistically significant manner). The assays of this embodiment of the invention therefore provide a method for identifying an agent that alters an inducible biological signaling pathway, which agent will be useful where specific manipulation of or intervention in a particular stimulus-inducible pathway may be desirable.

Candidate agents for use in a method for identifying an agent that alters (*e.g.*, increases or decreases in a statistically significant manner at least one phenotype associated with pathway induction) an inducible biological signaling pathway according to the present invention may be provided as "libraries" or collections of compounds, compositions or molecules. Such molecules typically include compounds known in the art as "small molecules" and having molecular weights less than $10^5$ daltons, preferably less than $10^4$ daltons and still more preferably less than $10^3$ daltons. For example, members of a library of test compounds can be administered to a plurality of samples, each containing at least one biological sample comprising a cell that comprises a PTP which has been identified as a reversibly modified (*e.g.*, oxidized) component of an inducible biological signaling pathway as provided herein, and then assayed for their ability to enhance or inhibit dephosphorylation of a PTP substrate by the PTP. Compounds so identified as capable of influencing PTP function (*e.g.*, phosphotyrosine

and/or phosphoserine/threonine dephosphorylation) are valuable for therapeutic and/or diagnostic purposes, since they permit treatment and/or detection of diseases associated with PTP activity. Such compounds are also valuable in research directed to molecular signaling mechanisms that involve PTP, and to refinements in the discovery and development of future PTP compounds exhibiting greater specificity.

Candidate agents further may be provided as members of a combinatorial library, which preferably includes synthetic agents prepared according to a plurality of predetermined chemical reactions performed in a plurality of reaction vessels. For example, various starting compounds may be prepared employing one or more of solid-phase synthesis, recorded random mix methodologies and recorded reaction split techniques that permit a given constituent to traceably undergo a plurality of permutations and/or combinations of reaction conditions. The resulting products comprise a library that can be screened followed by iterative selection and synthesis procedures, such as a synthetic combinatorial library of peptides (see *e.g.*, PCT/US91/08694, PCT/US91/04666, which are hereby incorporated by reference in their entireties) or other compositions that may include small molecules as provided herein (see *e.g.*, PCT/US94/08542, EP 0774464, U.S. 5,798,035, U.S. 5,789,172, U.S. 5,751,629, which are hereby incorporated by reference in their entireties). Those having ordinary skill in the art will appreciate that a diverse assortment of such libraries may be prepared according to established procedures, and tested using PTP according to the present disclosure.

THERAPEUTIC METHODS

One or more agents capable of altering an inducible biological signaling pathway and identified according to the above described methods may also be used to modulate (*e.g.*, inhibit or potentiate) PTP activity in a patient. As used herein, a "patient" may be any mammal, including a human, and may be afflicted with a condition associated with PTP activity or may be free of detectable disease. Accordingly, the treatment may be of an existing disease or may be prophylactic. Conditions associated with PTP activity include any disorder associated with cell proliferation, including cancer, graft-versus-host disease (GVHD), autoimmune

diseases, allergy or other conditions in which immunosuppression may be involved, metabolic diseases, abnormal cell growth or proliferation and cell cycle abnormalities.

For administration to a patient, one or more modulating agents are generally formulated as a pharmaceutical composition. A pharmaceutical composition may be a sterile aqueous or non-aqueous solution, suspension or emulsion, which additionally comprises a physiologically acceptable carrier (*i.e.*, a non-toxic material that does not interfere with the activity of the active ingredient). Such compositions may be in the form of a solid, liquid or gas (aerosol). Alternatively, compositions of the present invention may be formulated as a lyophilizate or compounds may be encapsulated within liposomes using well known technology. Pharmaceutical compositions within the scope of the present invention may also contain other components, which may be biologically active or inactive. Such components include, but are not limited to, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, stabilizers, dyes, flavoring agents, and suspending agents and/or preservatives.

Any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of the present invention. Carriers for therapeutic use are well known, and are described, for example, in *Remingtons Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro ed. 1985). In general, the type of carrier is selected based on the mode of administration. Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, intrathecal, rectal, vaginal, sublingual or parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal or intraurethral injection or infusion. For parenteral administration, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, kaolin, glycerin, starch dextrins, sodium alginate, carboxymethylcellulose, ethyl cellulose, glucose, sucrose and/or magnesium carbonate, may be employed.

A pharmaceutical composition (*e.g.*, for oral administration or delivery by injection) may be in the form of a liquid (*e.g.*, an elixir, syrup, solution, emulsion or suspension). A liquid pharmaceutical composition may include, for example, one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. The use of physiological saline is preferred, and an injectable pharmaceutical composition is preferably sterile.

The compositions described herein may be formulated for sustained release (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain an agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Within a pharmaceutical composition, a PTP modulating agent may be linked to any of a variety of compounds. For example, such an agent may be linked to a targeting moiety (*e.g.*, a monoclonal or polyclonal antibody, a protein or a liposome) that facilitates the delivery of the agent to the target site. As used herein, a "targeting moiety" may be any substance (such as a compound or cell) that, when linked to an

agent enhances the transport of the agent to a target cell or tissue, thereby increasing the local concentration of the agent. Targeting moieties include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Examples of antibody fragments are $F(ab')_2$, -Fab', Fab and F[v] fragments, which may be produced by conventional methods or by genetic or protein engineering. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Targeting moieties may be selected based on the cell(s) or tissue(s) toward which the agent is expected to exert a therapeutic benefit.

Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dosage and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient and the method of administration. In general, an appropriate dosage and treatment regimen provides the agent(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival). For prophylactic use, a dose should be sufficient to prevent, delay the onset of or diminish the severity of a disease associated with cell proliferation.

Optimal dosages may generally be determined using experimental models and/or clinical trials. In general, the amount of polypeptide present in a dose, or produced *in situ* by DNA present in a dose, ranges from about 0.01 μg to about 100 μg per kg of host, typically from about 0.1 μg to about 10 μg. The use of the minimum dosage that is sufficient to provide effective therapy is usually preferred. Patients may generally be monitored for therapeutic or prophylactic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those having ordinary skill in the art. Suitable dose sizes will vary with the size of the patient, but will typically range from about 10 mL to about 500 mL for 10-60 kg animal.

The following Examples are offered for the purpose of illustrating the present invention and are not to be construed to limit the scope of this invention.

# EXAMPLES

## EXAMPLE 1

### REVERSIBLE INACTIVATION OF PTPS IN RAT-1 CELLS BY HYDROGEN PEROXIDE

Cell culture, transient transfection, immunoprecipitation and immunoblotting: Rat-1 fibroblasts (American Type Culture Collection, Manassas, VA) were routinely maintained in DMEM supplemented with 10% FBS, 1% glutamine, 100 U/ml penicillin and 100 μg/ml streptomycin (all reagents Sigma, St. Louis, MO, unless otherwise noted). For stimulation with $H_2O_2$ and peptide growth factors, cells were plated in media containing 10% FBS for 48 hours, then serum-starved for 16 hours before treatment. For transient transfection, Rat-1 cells were plated in DMEM medium supplemented with 10% FBS, for 16 hours. The culture medium was replaced by OptiMEM™ (Invitrogen Life Technologies, Inc. Gaithersburg, MD) without serum, then plasmid (5 μg/dish) was introduced into cells by LipofectAMINE™ and PLUS™ reagents (Life Technologies), according to the manufacture's recommendations. The transfection efficiency was routinely 40%.

For immunoprecipitation, cells were rinsed with ice-cold PBS, then lysed in ice-cold 20 mM Hepes (pH 7.5), 1% NP-40, 150 mM NaCl, 10% glycerol, 200 μM $Na_3VO_5$ and protease inhibitors (25 μg/ml of aprotinin and leupeptin). Antibodies having the indicated specificities were purchased from the following suppliers: SHP-1 (C-19), SHP-2 (C-18) and PI3K (Z-8), Santa Cruz Biotecnology, Santa Cruz, CA; phospho-MAPK and MAPK, Cell Signaling, Inc. (Beverly, MA); GAP, BD Transduction Laboratories (Lexington, KY); and pTyr mAb PT66, Sigma, St. Louis, MO. The anti-pTyr antibody G104 was described previously (Garton et al., 1997 *Oncogene 15*, 877-885). Anti-PDGFRβ antibody (Ab-X) was a gift from Dr. Daniel DiMaio at Yale University (Irusta and DiMaio, 1998 *EMBO J 17*, 6912-6923). Anti-human G-CSF receptor (G-CSFR) antibody was provided by Dr. Toshio Hirano at Osaka University, Japan (Fukada et al., 1996 *Immunity 5*, 449-460). Lysate (400 μg) was incubated with 5 μg of antibody conjugated to protein A/G-Sepharose (Amersham Pharmacia, Arlington Heights, IL) for 2 hours at 4 °C. For immunoblotting, aliquots of

total lysates (30 μg per sample) or immunoprecipitates were subjected to SDS-PAGE and transferred to nitrocellulose filters, which were incubated with appropriate primary and secondary antibodies and the specific signals were visualized by the ECL detection system (Amersham Pharmacia).

To determine whether ROS stimulated intracellular tyrosine phosphorylation through the oxidation and inhibition of cellular PTPs, a modified in-gel PTP activity assay was devised, as follows: As substrate, poly (4:1) Glu-Tyr (Sigma) was labeled with [$\gamma$-$^{32}$P]-ATP using the GST-FER fusion PTK, as described previously (Shen et al., 1998 *J. Biol. Chem.* 273:6474-81). The labeled substrates were used within three weeks to limit the variation of its specific activity from experiment to experiment. The lysis buffer (25 mM $CH_3COONa$, 1% NP-40, 150 mM NaCl, 10% glycerol, pH 5.5) was degassed at 4 °C for overnight, before catalase and superoxide dismutase (both 100 μg/ml), protease inhibitors and 10 mM iodoacetic acid (IAA) were added. Following stimulation, cells were lysed under anaerobic conditions in an argon chamber. Lysates (25 μg) were processed as described herein and an "in-gel" phosphatase assay (Burridge and Nelson, 1995) was conducted using SDS-PAGE gels containing a radioactively-labeled substrate (1.5 x $10^6$ cpm/20 ml gel solution, approximately 2 μM p-Tyr).

Cells were triggered with the appropriate stimulus and harvested under anaerobic conditions in lysis buffer containing IAA. Those PTPs that had not encountered ROS in the cell became irreversibly inactivated by alkylation of their active site Cys with IAA. However, in contrast, any PTPs in which the active site Cys had been oxidized in response to the stimulus were resistant to alkylation. For the "in-gel" phosphatase assay, a 10% SDS-PAGE gel was cast containing a radioactively-labeled substrate. An aliquot of cell lysate was subjected to SDS-PAGE and proteins in the gel were sequentially denatured, then renatured in the presence of reducing reagents. Under these conditions, the activity of the PTPs in which the active site Cys had been subjected to stimulus-dependent oxidation to sulfenic acid was recovered, whereas those that were not oxidized in response to the initial stimulus, and were irreversibly alkylated in the lysis step, remained inactive. The reaction was then terminated by fixing, staining and destaining the gel. Finally the gel was dried and exposed to film.

The presence of a PTP was visualized by substrate dephosphorylation, as the appearance of a clear, white area on the black background of labeled substrate. As shown in Fig. 1, the PTPs that exhibited catalytic phosphatase activity in this assay would be those originally protected from post-lysis alkylation by a stimulus-dependent modification at the active site Cys, which was reversed by DTT, consistent with oxidation of the Cys to sulfenic acid.

The data shown in Fig. 2A illustrate that iodoacetic acid (IAA) in the lysis buffer effectively inactivated PTPs in a lysate of Rat-1 cells (lane 2, compared to lane 1), via irreversible alkylation of the invariant, active site Cys residue of these enzymes (Zhang and Dixon, 1993 *Biochemistry* 32:9340-45). Fig. 2A shows the results when serum-deprived Rat-1 cells were exposed to various concentrations of $H_2O_2$ for 1 min, harvested and lysed in the absence (lane 1) or presence (lanes 2-7) of 10 mM IAA. Aliquots of lysate were subjected to the in-gel PTP assay. When $H_2O_2$ was added to the culture media, it gained rapid access to the intracellular environment and within 1 minute the active site Cys residue of various PTPs was oxidized, thereby protecting them from alkylation by IAA (lanes 3 - 7, Fig. 2A). Furthermore, 200 μM $H_2O_2$ was sufficient to oxidize all of the PTPs detectable in this assay format, but more extensive oxidation occurred at higher concentrations of $H_2O_2$ (Fig. 2A).

Fig. 2B shows results obtained when tyrosine phosphorylated proteins were immunoprecipitated from lysates of $H_2O_2$-treated cells with Ab PT-66, then immunoblotted with anti-pTyr Ab (G104). The tyrosine phosphorylation of proteins of ~120 kDa and 70 kDa was induced in a dose-dependent fashion coincident with exposure of cells to $H_2O_2$ (Fig. 2B), suggesting a link between oxidation/inhibition of PTPs and enhanced tyrosine phosphorylation in Rat-1 cells. This stimulation also triggered the phosphorylation of ERK MAP kinases (MAPKs). N-acetyl cysteine (NAC), a widely used ROS scavenger, blocked PTP oxidation and inactivation induced by 200 μM $H_2O_2$, thus confirming that the effects on PTP activity shown in the in-gel assay were due to $H_2O_2$-induced intracellular oxidation (Fig. 2C). Fig. 2C depicts the results obtained when cells were preincubated in the absence or presence of 30 mM NAC for 40 minutes and excess NAC removed by two washes with fresh culture medium, after which the Rat-1 cells were exposed to 200 μM $H_2O_2$ and lysed in the

presence of 10 mM IAA at the indicated times. Lysates were subjected to the in-gel PTP assay.

In addition, depletion of the cellular pool of glutathione (GSH) by exposure of the cells to L-buthionine-SR-sulfoximine (BSO), a specific inhibitor of γ-glutamylcysteine synthetase, markedly attenuated the recovery of PTP activity following removal of an $H_2O_2$ stimulus (Fig. 2D). To obtain the data presented in Fig. 2D, Rat-1 cells were serum-starved in the absence or presence of 2.5 mM BSO for 16 h. $H_2O_2$ (200 μM) was added for 2 minutes, then removed by washing the cells with fresh culture media. Incubation was then continued until harvesting in lysis buffer containing 10 mM IAA at the times indicated. Oxidized PTPs were visualized by the in-gel phosphatase activity assay. Arrows indicate PTPs for which reduction/reactivation exhibited dependence on intracellular GSH. Stimulation with $H_2O_2$ led to oxidation of several PTPs (lane 2), which were quickly reduced once $H_2O_2$ was removed (Fig. 2D, lanes 3-6). Recovery was essentially complete within 10-20 minutes of removal of $H_2O_2$. However, when the same analysis was performed on Rat-1 cells that had been subjected to pretreatment with BSO, oxidation persisted even 30 minutes after removal of $H_2O_2$ (Fig. 2D lanes 8-12). Surprisingly, these observations provide the first demonstration that multiple PTPs may be oxidized and inactivated by ROS in a cellular environment.

## EXAMPLE 2

## $H_2O_2$-INDUCED MITOGENIC SIGNALING ASSOCIATED WITH PTP INACTIVATION

In order to explore the importance of oxidation and inhibition of PTP function for ROS-induced mitogenesis, the effects of $H_2O_2$ and the synthetic ROS t-butyl hydroperoxide (t-BHP) were tested. Initially, the susceptibility of an activated mutant form of SHP-2 (E76A) to alkylation by IAA was compared following treatment with either $H_2O_2$ or t-BHP. Using the modified in-gel PTP assay described in Example 1, SHP-2, which had been pre-treated with PBS, was inactivated by IAA (lane 2, compared to lane 1, Fig. 3A), whereas oxidation with $H_2O_2$ protected SHP-2 from alkylation (Fig. 3A). Briefly, purified SHP-2 (E76A mutant) was incubated with PBS,

$H_2O_2$ or t-BHP at 37 °C for 5 mins. Aliquots were then incubated at room temp for a further 5 minutes, either in the absence (- IAA) or presence (+IAA) of 4 mM IAA, and subjected to the in-gel PTP activity assay (1 ng SHP-2/lane). Even at 2 mM $H_2O_2$, SHP-2 was not irreversibly oxidized since its activity was recovered in the in-gel assay (Fig. 3A). In contrast, t-BHP was unable to oxidize and inactivate SHP-2 *in vitro* and thus did not protect the invariant Cys residue of SHP-2 from alkylation (Fig. 3A).

The effects of $H_2O_2$ and t-BHP on inactivation of PTPs and activation of MAPK signaling pathways were next compared in a cellular context. Intracellular ROS were measured using 2',7'-dichlorofluorescein diacetate ($H_2$DCFDA) and 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate (CM-$H_2$DCFDA) (all fluorescent ROS indicators from Molecular Probes, Eugene, OR) either by fluorescence microscopy, using a Zeiss Axiovert 405M inverted microscope equipped with a fluorescence attachment and digital camera, or by cell sorting, using a FACSCalibur System (Coulter Instruments, Hialeah, FL), according to the manufacturer's recommendations. Rat-1 cells were pre-loaded with 20 μM $H_2$DCFDA in the dark for 20 mins, then exposed to $H_2O_2$ and t-BHP (both 200 μM) for 5 mins. Images of ROS-induced DCF fluorescence are shown at magnification 400X (Fig. 3B upper panel). Cells (1 x $10^5$) that underwent the same treatment as above were harvested and resuspended in Hanks' solution, then immediately subjected to flow cytometric analysis to measure ROS-induced DCF fluorescence. The basal peak indicates background fluorescence, whereas the rightward shifted peak indicates ROS-induced DCF fluorescence (Fig. 3B, lower panels). Initially, fluorescence microscopy of Rat-1 cells, preloaded with $H_2$DCFDA, showed that treatment with either $H_2O_2$ or t-BHP led to rapid oxidation and the appearance of the fluorescent derivative, DCF (upper panels, Fig. 3B). Furthermore, upon flow cytometric analysis no quantitative difference was observed between the $H_2O_2$- and t-BHP-induced shift of fluorescence (Fig. 3B, lower panels). However, when the ability to oxidize PTPs in the cells was examined, reproducible inactivation of PTPs was detected in response to $H_2O_2$ but not in response to t-BHP (Fig, 3C). Cells were exposed to $H_2O_2$ and t-BHP (each at 200 μM) for the indicated times, lysed in the presence of 10 mM IAA and oxidized PTPs were visualized in the in-gel PTP activity assay.

$H_2O_2$ and t-BHP were next compared for their effects on tyrosine phosphorylation of cellular proteins, and on activation of MAPKs. As shown in Fig. 3D, after exposure to $H_2O_2$ and t-BHP (each at 200 μM), lysates were prepared and pTyr proteins were immunoprecipitated with Ab PT-66, then immunoblotted with anti-pTyr Ab G104 (Fig. 3D, upper panel). An aliquot of lysate from each treatment group was immunoblotted with anti-phospho-MAPK Ab and subsequently with anti-MAPK Ab (Fig. 3D, lower panel). As shown in Fig. 3D, the inactivation of PTPs by $H_2O_2$ was associated with enhanced tyrosine phosphorylation and mitogenic signaling. In contrast, t-BHP elicited less pronounced effects on tyrosine phosphorylation and was unable to activate MAPKs (Fig. 3D), presumably due to its inability to oxidize and inactivate the PTPs. Without wishing to be bound by theory, these results are consistent with a role of PTP inactivation in the mitogenic effects of ROS.

## EXAMPLE 3

## OXIDATION OF A 70 KDA PTP ASSOCIATED WITH PDGF-INDUCED MITOGENIC SIGNALING IN RAT-1 CELLS AND IDENTIFICATION OF THE 70 KDA PTP AS SHP-2

As described above, treatment of Rat-1 cells with $H_2O_2$ led to inactivation of multiple PTPs (Figs. 2-3). This Example describes studies to determine whether the production of ROS in response to physiological stimuli also resulted in oxidation and inactivation of members of the PTP family, and whether there was specificity in the response. Initially examined were the effects of PDGF, a peptide growth factor, which has been shown to produce ROS in various cell types (Bae et al., 2000; Sundaresan et al., 1995). Preliminary experiments showed that treatment of Rat-1 cells with PDGF resulted in a rapid increase in the tyrosine phosphorylation of cellular proteins and the enhanced phosphorylation of MAPKs. Lysates of PDGF-stimulated Rat-1 cells were then analyzed using the modified in-gel PTP activity assay described above. The results, as shown in Figure 4, demonstrated that PDGF stimulation induced a rapid and transient oxidation of a PTP having an apparent molecular mass of ~70 kDa. Serum-starved Rat-1 cells were exposed to 50 ng/ml

PDGF-BB for the times indicated (Fig. 4A). Lysates were prepared in the presence of 10 mM IAA and subjected to the in-gel PTP assay. The arrow indicates a 70k PTP that was transiently oxidized following stimulation of Rat-1 cells with PDGF. The result shown is representative of four independent experiments. Oxidation of this 70 kDa PTP was reversible, reaching a maximum at 5 minutes, followed by marked reduction, almost to basal levels, within 20 minutes of PDGF treatment (Fig. 4A).

A possible role of oxidation/inactivation of the 70k PTP in regulating PDGFR-mediated signaling was next investigated by testing the effects of the antioxidant NAC. Cells were incubated for 40 minutes in the presence or absence of 30 mM NAC prior to PDGF stimulation. Excess NAC was removed prior to addition of PDGF (50 ng/ml). PDGF-induced oxidation of the 70k PTP, which was impaired in the presence of NAC (Fig. 4B, arrow), was visualized by the modified in-gel PTP assay. Then the modified in-gel PTP assay was used to examine the effects of the growth factor on the activity of the 70k PTP. When the levels of PDGF-induced ROS were reduced by pretreatment with NAC, oxidation of the 70k PTP was markedly attenuated (Fig. 4B). Furthermore, the ligand-induced tyrosine phosphorylation of the PDGFR was greatly diminished, and the activation of MAPKs was completely eliminated, in NAC-treated cells (Fig. 4C). Cells were treated with NAC and PDGF as described above. PDGFR was immunoprecipitated from lysates with Ab-X and immunoblotted with anti-pTyr Ab G104. The same filter was subsequently re-probed with Ab-X (Fig. 4C, upper panels). Aliquots of cell lysate from each treatment were immunoblotted with anti-phosho-MAPK Ab and re-probed with anti-MAPK Ab (Fig. 4C, lower panels). These data suggest that the rapid, transient inactivation of 70k PTP may be important for concomitant PDGFR-mediated phosphorylation and mitogenic signaling.

In attempting to identify the 70k PTP that was oxidized following PDGF stimulation, attention was drawn to the SH2 domain-containing PTP, SHP-2. This PTP has been shown to be associated with tyrosine phosphorylated PDGFR (Lechleider et al., 1993 *J. Biol. Chem.* 268:21478-81). In addition, the apparent molecular weight of SHP-2 on SDS-PAGE is similar to that of the PDGF-responsive 70k PTP detected in Fig. 4. Initially, it was confirmed that SHP-2 could be recruited by the ligand-activated PDGFR in Rat-1 cells. Serum-starved Rat-1 cells were exposed to PDGF (50 ng/ml)

for the indicated times (Fig. 5A). The PDGFR and associated proteins were immunoprecipitated with antibody Ab-X, and pTyr proteins visualized by immunoblotting with anti-pTyr Ab G104 (Fig. 5A, upper panel). The same filter was re-probed with anti-PDGFR, anti-SHP-2, anti-GAP and anti-p85 PI3K Abs. The positions of PDGFR (Fig. 5A, solid arrow) and SHP-2 (Fig. 5A, open arrow) are indicated. As shown in Fig. 5A (upper panel), a tyrosine phosphorylated protein of ~70 kDa by SDS-PAGE associated rapidly with the PDGFR in response to ligand activation. Furthermore, immunoblotting was used to show that SHP-2 comigrated with this 70k phosphoprotein (Fig. 5A, lower panels). The complex between PDGFR and SHP-2 persisted for up to 20 minutes after stimulation, then the level of association decreased (Fig. 5A, lower panels).

To test whether SHP-2 was the 70k PTP that was oxidized following PDGF stimulation, SHP-2 protein was immunodepleted from cell lysates with increasing amounts of anti-SHP-2 antibody, and the supernatants were subjected to the modified in-gel PTP assay. Rat-1 cells, either untreated (-) or stimulated with 50 ng/ml PDGF (+), were harvested in lysis buffer containing 10 mM IAA. Lysates were incubated with antibody to either SHP-2 or SHP-1 and subjected to an in-gel PTP assay (Fig. 5B, upper panel). The arrow denotes the position of the 70k PTP that was inactivated in response to PDGF and immunodepleted from cell lysates with antibodies to SHP-2. The lower panel of Fig. 5B illustrates an immunoblot to show the immunodepletion of SHP-2. As shown in Fig. 5B, anti-SHP-2 antibody depleted the 70k PTP from Rat-1 cell lysates, whereas an anti-SHP-1 antibody control did not. These data identify SHP-2 as a PTP that was rapidly oxidized and inactivated following PDGF stimulation.

Association of other SH2 domain-containing proteins with activated PDGFR was also examined. It has been shown that SHP-2 dephosphorylates the PDGFR on the autophosphorylation sites that function as binding sites for GTPase-activating protein (GAP) and phosphatidylinositol 3 kinase (PI3K) (Klinghoffer and Kazlauskas, 1995 *J. Biol. Chem.* 270:22208-17) (*see also* Kazlauskas et al., 1992 Mol. Cell Biol. 12:2534-44). However, both GAP and the p85 subunit of PI3K were recruited by PDGFR rapidly after ligand stimulation, even though SHP-2 was

associated with the receptor at this time (Fig. 5A). These results suggest that oxidation and inactivation of SHP-2 in response to PDGF may be important for permitting recruitment of GAP and PI3K by the activated PDGFR. Interestingly, GAP and PI3K dissociated from the receptor by 10 minutes after PDGF stimulation (Fig. 5A), coincident with dephosphorylation of PDGFRβ (Fig. 5A) and reactivation of SHP-2 (Fig. 4A).

## EXAMPLE 4

## SPECIFICITY OF ROS PRODUCTION AND SHP-2 OXIDATION AND INACTIVATION IN RESPONSE TO GROWTH FACTOR STIMULATION

SHP-2 was one of the first PTPs to be recognized as capable of both negative signaling (by antagonizing PTK function) and positive signaling following a PTP-mediated dephosphorylation event, playing such a role, for example, in the context of EGF and FGF receptor signaling (Bennett et al., 1996 *Mol. Biol. Cell* 16:1189-1202; Saxton et al., 1997 *EMBO J.* 16:2352-64). The data described above, showing oxidation and inhibition of SHP-2 in response to PDGF, appear to be indicative of a negative role in signaling. This example describes additional characterization of a PTP response to a stimulus that induces a biological signaling pathway.

Treatment of Rat-1 cells with PDGF triggered production of intracellular ROS (Fig. 6A), concomitant with oxidation and inactivation of SHP-2 (Fig. 6B). In contrast, ROS production was not detected in response to either EGF or FGF (Fig. 6A). Rat-1 cells were incubated with 20 μM CM-$H_2$DCFDA in the dark for 20 mins, then exposed to peptide growth factors (50 ng/ml) for an additional 10 mins. Images of ROS-induced DCF fluorescence are shown at 50X magnification. (Fig. 6A) The data are representative of 4 independent experiments. In Fig. 6B, Rat-1 cells were exposed to peptide growth factors for the indicated times, lysed in the presence of 10 mM IAA, and oxidized PTPs were visualized by the in-gel PTP assay. In this assay, too, oxidation and inhibition of SHP-2 was observed following PDGF stimulation of the cells but not following exposure of these cells to EGF or FGF. EGF, FGF and PDGF

all activated MAPK to a similar extent in Rat-1 cells (Fig. 6C). Aliquots of cell lysate from each treatment group were immunoblotted with anti-phospho-MAPK Ab and re-probed with anti-MAPK Ab. These results indicate that, of the stimuli examined in Rat-1 cells, transient oxidation and inactivation of SHP-2 is a specific response to PDGF, consistent with differences in the function of SHP-2 in these distinct growth factor signaling pathways.

The next set of experiments demonstrated that the PDGFR-associated pool of SHP-2 was susceptible to oxidation and inactivation. Recent studies have suggested that a Rac1-associated, plasma membrane-bound NADPH oxidase is responsible for PDGF-induced generation of ROS in non-phagocytic cells (Bae et al., 2000). In light of the short half-life of such ROS, it is possible that their influence on PTPs may be spatially restricted to the subcellular regions proximal to their production.

In preliminary studies only ~10% of the total population of SHP-2 was recruited into a complex with the PDGFR following ligand stimulation in Rat-1 cells. To examine whether this recruitment was required for oxidation and inactivation of SHP-2 in response to PDGF, mutant forms of the PDGFR were constructed that were deficient in their association with SHP-2. Chimeric cell surface signal transduction receptors were also constructed which consisted of the extracellular segment of human granulocyte colony stimulating factor (G-CSF) receptor and the transmembrane and cytoplasmic segments of human PDGFR. The ability of these mutant PDGFRs to induce oxidation of the PTP in response to ligand was then tested.

Full length cDNA encoding wild type (WT) and Y1009F mutant forms of human PDGFRβ was provided by Dr. Jonathan Cooper (Fred Hutchinson Cancer Center, Seattle, WA; (Kashishian and Cooper, 1993 *Mol. Biol. Cell* 4:49-57)). The cDNA encoding the extracellular segment of human G-CSFR was a gift from Dr. Shigekazu Nagata (Osaka University, Japan; (Fukada et al., 1996)). Chimeric receptors comprising the extracellular segment of G-CSFR fused to the transmembrane and intracellular (WT and Y1009F) segments of PDGFRβ were constructed in the pcDNA3.1A vector (Invitrogen) by standard PCR protocols then inserted into a pRK5 expression vector for transient transfection experiments. The integrity of the constructs was confirmed by sequencing. These chimeric receptors permitted examination of G-

CSF-induced recruitment of SHP-2 to the chimeric receptors and signaling in Rat-1 cells, which do not express endogenous G-CSF receptor (G-CSFR), while avoiding activation of endogenous PDGFR. The autophosphorylation site at Y 1009 of human PDGFR has been shown to be the major docking site for the N-terminal SH2 domain of SHP-2 (Lechleider et al., 1993).

Expression constructs encoding chimeric receptors comprising either wild type (WT) or Y1009F forms of the PDGFR intracellular segment were transiently transfected into Rat-1 cells. Upon stimulation with G-CSF, both WT and Y1009F chimeric receptors were tyrosine phosphorylated (Fig. 7A). Although both receptors were activated following treatment with G-CSF, only the WT recruited SHP-2, which was recovered in immune-complexes precipitated with antibodies to the intracellular segment of the PDGFR (Fig. 7A). Using the modified in-gel PTP assay, WT chimeric receptors triggered rapid oxidation and inactivation of SHP-2 in response to G-CSF stimulation. Rat-1 cells were transiently transfected with plasmids expressing WT or Y1009F mutant G-CSFR/PDGFR chimeric receptor, or with a plasmid encoding Green Fluorescence Protein (GFP) as a control for expression. After exposure to 100 ng/ml G-CSF for 5 min, the chimeric receptors were immunoprecipiated from lysates with antibody Ab-X and immunoblotted with anti-pTyr Ab G104. (Fig. 7A) Immunoprecipitation of the receptors was verified by immunoblotting with Ab-X. The same filter was stripped and reprobed with anti-SHP-2 Ab. Expression of the chimeric receptors was verified by immunoblotting an aliquot of each lysate with Ab-X, which recognizes the intracellular segment of the PDGFR, and subsequently with anti-G-CSFR Ab, which recognizes the extracellular segment of chimeric receptors, as also shown in Fig. 7A.

Next, transfected Rat-1 cells were treated with G-CSF for the indicated times, lysed in the presence of 10 mM IAA and the lysates subjected to an in-gel PTP assay. (Fig. 7B) Activation of Y1009F mutant receptors did not induce oxidation of SHP-2 (Fig. 7B), suggesting according to non-limiting theory that recruitment of SHP-2 by activated, chimeric PDGFR was required for oxidation of the PTP by ROS generated in response to ligand. The arrow denotes the position of SHP-2.

Using the G-CSF:PDGF receptor chimeras, a time course of exposure to G-CSF illustrated that both WT and Y1009F, SHP-2 docking site mutant receptors were rapidly tyrosine phosphorylated following ligand stimulation. However, whereas tyrosine phosphorylation of the WT receptor was transient, the mutant receptor was maintained at a higher level of phosphorylation throughout the time course (Fig. 7C). The differences were particularly striking at the later time points, following 20 and 30 minutes of ligand stimulation. As shown in Fig. 7C, the WT and mutant chimeric receptors were immunoprecipitated at the indicated times and immunoblotted with anti-pTyr Ab (G104). The same filter was re-probed with anti-PDGFR Ab-X.

The phosphorylation status of MAPKs in the cell lysates was also investigated by immunoblotting analysis with antibodies specific for the phosphorylated and dephosphorylated forms of MAPK. Maximal phosphorylation of p42 and p44 ERKs following 20 minutes of stimulation (Fig. 7D). Fig. 7D shows the results obtained when aliquots of lysate from each treatment group were also subjected to immunoblotting with anti-phosho-MAPK Ab, and then re-probed with anti-MAPK Ab. However, both the extent and duration of ERK phosphorylation was higher in cells expressing the mutant receptor, which was deficient in binding of SHP-2, compared to those expressing the wild type receptor (Fig. 7D & E). As shown in Fig. 7E, densitometric analysis of the gel image of Fig. 7D illustrates the ratio of phosphorylated (upper panel of 7D) over total (lower panel of 7D) MAPK. Without wishing to be bound by theory, these results suggest that recruitment of SHP-2 into the PDGF receptor-containing signaling complex is important for down-regulation of both receptor tyrosine phosphorylation and activation of MAPK, and that oxidation and inhibition of SHP-2 in the early phase of the response to PDGF is important for establishment of the signaling response.

## EXAMPLE 5

## PRIOR TREATMENT OF CELLS WITH A PTP ACTIVE SITE-BINDING AGENT PROTECTS AGAINST IAA-MEDIATED PTP INACTIVATION

An in-gel protection assay was developed to show that a small molecule PTP inhibitor could bind to the active site of the PTP and protect the active site cysteine

from alkylation or from other irreversible modifications. An independently developed PTP inhibitor was shown to inhibit PTP catalytic activity and characterized by X-ray crystallography as a PTP active site-binding agent. This PTP inhibitor, referred to here as ASBA-1, was used to demonstrate that the PTP inhibitor could specifically bind to a PTP in an activated blood cell.

Peripheral blood mononuclear lymphocytes were purified from human blood. In 5 ml media (RPMI), 2 x $10^7$cells were incubated in 50 μM ASBA-1 (PTP specific inhibitor) for 90 minutes and stimulated with phytohemagglutinin (PHA, 0.5 μl of 5.0 mg/ml stock) for 2, 10 or 30 min. Cells were pelleted, washed and lysed in buffer in the presence or absence of 50 mM iodoacetic acid (IAA) in extraction buffer (50mM Tris, pH 7.5; 1mM EDTA; 1mM EGTA; 0.25% Triton X-100; 1ug/mL pepstatin, aprotinin, and leupeptin; 1mM benzamidine). Desalted proteins were separated on a 2ml Source Q anion exchange column (Amersham Pharmacia Biotech) using a 0-1M NaCl gradient in 20mM Tris, pH 7.5; 1mM EDTA; 0.05% Triton X-100. Samples of each fraction were analyzed by the in-gel PTP assay (described above) and the results are shown in Figure 9. At least two IAA-insensitive, PTP activity bands were observed from ASBA-1-treated cells, following autoradiography of the dried gel (Fig. 9, left panel). In samples from cells in which these proteins were not protected by ASBA-1 pretreatment, the PTPs were inactivated by IAA and PTP activity was not observed in the corresponding gel region using the in-gel PTP activity assay (Fig. 9, right panel). Therefore, and according to non-limiting theory, specific binding of ASBA-1 to the active sites of at least two PTPs in these cells prevented complete inactivation of the PTPs by IAA.

## EXAMPLE 6

## INSULIN SIGNALING MEDIATED BY ROS PRODUCTION

The role of intracellular production of ROS (*e.g.*, $H_2O_2$) in insulin-mediated signal transduction was examined. Rat-1 fibroblasts were cultured and then serum starved for 16 hours as described in Example 1. The cells were preloaded with 5 μM CM-$H_2$DCFDA (Molecular Probes, Eugene, OR, Cat. No. D-399) in the dark for

15 min and then exposed to 50 nM insulin for 10 minutes. Images of ROS-induced DCF fluorescence were captured by fluorescence microscopy using a Zeiss Axiovert 405M inverted microscope equipped with a fluorescence attachment and digital camera (see Example 2), and are shown at 50x magnification in Figure 10A.

Ectopic expression of catalase, which suppresses intracellular $H_2O_2$ production, impaired both tyrosine phosphorylation of the β-subunit of the insulin receptor (IR- β) and the phosphorylation of the downstream signaling molecule PKB/Akt in response to insulin stimulation. Rat-1 cells were transiently transfected as described in Example 1 with different quantities of plasmid encoding human catalase (a gift from Dr. Toren Finkle, NIH, Bethesda MD) or with empty vector. Two days after transfection, cells were serum-deprived, then stimulated with 50 nM insulin (INS) for 10 min. The cells were lysed in 20 mM Hepes (pH 7.5), 1% NP-40, 150 mM NaCl, 10% glycerol, and 200 μM $Na_3VO_4$ containing 25 μg/ml each of aprotinin and leupeptin. Immunoblotting and immunoprecipitation were then performed essentially as described in Example 1. Catalase expression was verified by immunoblotting with an anti-catalase antibody (Calbiochem®, San Diego, CA) as shown in Figure 10B (top panel). The IR-β subunit was immunoprecipitated from 400 μg of the cell lysate with antibody 29B4 (Santa Cruz). The lysate was separated by SDS-PAGE and then immunoblotted with anti-$pYpY^{1162/1163}$ (Biosource International, Camarillo, CA) to examine the phosphorylation status of the receptor. The immunoblot was subsequently probed with anti-IR-β antibody clone C-19 (Santa Cruz) as a loading control (Figure 10B, middle panel). An aliquot of lysate (30 μg) was subjected to immunoblotting with anti-phospho-PKB/AKT antibody (Cell Signaling). The same filter was then stripped and re-probed with anti-PKB/AKT antibody (Cell Signaling) as a loading control (Figure 10B, bottom panel).

## EXAMPLE 7

## INSULIN INDUCES TRANSIENT OXIDATION OF PTP1B AND TC45

The effect of insulin-induced $H_2O_2$ production on PTP oxidation was examined using the modified in-gel PTP assay essentially as described in Example 1. Serum-starved Rat-1 cells were exposed to 50 nM insulin for 2, 5, 10, 20, and 30 minutes. Lysates were prepared under anaerobic conditions in the presence of 10 mM IAA and then subjected to in-gel PTP assays. The substrate incorporated into the SDS-PAGE gels for these assays was $^{32}$P-labeled reduced, carboxamidomethylated and maleylated lysozyme (RCML) (1.5 x $10^6$ cpm/20 ml gel solution, ~2 μM p-Tyr). Figure 11A shows that a PTP having an approximate molecular weight of 50 kDa and a PTP with an approximate molecular weight of 45 kDa were transiently oxidized in response to insulin.

The oxidized 45 kDa and 50 kDa PTPs were identified as TC-45 and PTP1B, respectively, by immunodepletion and immunoblotting. Total cell lysates were prepared as described in Example 1. Lysate (400 μg) was incubated with normal IgG, anti-PTP1B antibody (FG6, LaMontagne et al., *Mol. Cell. Biol.* 18:2965-75 (1998)), or anti-TC45 antibody (1910H, Lorenzen et al., *J. Cell. Biol.* 131:631-43 (1995)) coupled to protein G-Sepharose™ beads (Amersham Biosciences). After the immunoprecipitation step, the immune complexes and supernatants were collected and subjected to in-gel PTP assays. Immunodepletion of the 50 kDa PTP from the lysate with anti-PTP1B antibody is shown in Figure 11B, and immunodepletion of the 45 kDa PTP with antibody specific for TC45 is shown in Figure 11C. Cell lysate prior to immunodepletion is represented in the lane marked "Lys" in Figures 11B and 11C. Total cell lysate and supernatants were separated by SDS-PAGE, transferred to nitrocellulose membranes, and immunoblotted with either anti-PTP1B antibody (Fig. 11B) or anti-TC45 antibody (Fig. 11C). The immunoblots show that each PTP protein is depleted after immunoprecipitation with the specific antibody. The same immunoblots were subsequently reprobed with anti-SHP-2 antibody to illustrate that comparable amounts of polypeptide were loaded onto each gel.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

What is claimed is:

1. A method for identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell, comprising:

contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus under conditions and for a time sufficient to induce reversible oxidation of at least one protein tyrosine phosphatase in the cell;

isolating anaerobically the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell.

2. The method of claim 1 wherein the protein tyrosine phosphatase is selected from the group consisting of SHP-2, PTP1B, and TC45.

3. The method of claim 1 wherein the protein tyrosine phosphatase is selected from the group consisting of PTP1B, PTP-PEST, PTPγ, LAR, MKP-1, CRYPα, PTPcryp2, DEP-1, SAP1, PCPTP1, PTPSL, STEP, HePTP, PTPIA2, PTPNP, PTPNE6, PTPμ, PTPX1, PTPX10, SHP-1, SHP-2, PTPBEM1, PTPBEM2, PTPBYP, PTPesp, PTPoc, PTP-PEZ, PTP-MEG1, MEG2, LC-PTP, TC-PTP, TC45, CD45, LAR, cdc14, RPTP-α, RPTP-ε, RKPTP, LyPTP, PEP, BDP1, PTP20, PTPK1, PTPS31, PTPGMC, GLEPP1, OSTPTP, PTPtep, PTPRL10, PTP2E, PTPD1, PTPD2, PTP36, PTPBAS, PTPBL, BTPBA14, PTPTyp, HDPTP, PTPTD14, PTPα, PTPβ, PTPδ, PTPε, PTPκ, PTPλ, PTPμ, PTPρ, PTPψ, PTPϕ, PTPζ, PTPNU3 and PTPH1.

4. The method of claim 1 wherein the protein tyrosine phosphatase is a protein tyrosine phosphatase as presented in Figure 8.

5. The method of claim 1 wherein the protein tyrosine phosphatase is a dual specificity phosphatase.

6. The method of claim 1 wherein the protein tyrosine phosphatase substrate comprises phosphorylated poly-(4:1)-Glu-Tyr.

7. The method of claim 6 wherein the phosphorylated poly-(4:1)-Glu-Tyr comprises $^{32}P$.

8. The method of claim 1 wherein the detectably labeled protein tyrosine phosphatase substrate comprises a reporter molecule selected from the group consisting of a fluorophore, a radionuclide, a chemiluminescent agent, an enzyme, an immunologically detectable epitope and a chromaphore.

9. The method of claim 8 wherein the fluorophore is selected from the group consisting of fluorescein, rhodamine, Texas Red, AlexaFluor-594, AlexaFluor-488, Oregon Green, BODIPY-FL and Cy-5.

10. The method of claim 1 wherein the protein tyrosine phosphatase substrate comprises a polypeptide sequence derived from a protein selected from the group consisting of PDGF receptor, VCP, $p130^{cas}$, EGF receptor, p210 bcr:abl, MAP kinase, Shc, insulin receptor, lck, T cell receptor zeta chain, and reduced and carboxyamidomethylated and maleylated lysozyme (RCML).

11. The method of claim 1 wherein the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is an alkylating agent.

12. The method of claim 1 wherein the sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is selected from the group consisting of iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog and N-ethylmaleimide.

13. The method of claim 1 wherein the cell is a mammalian cell.

14. The method of claim 13 wherein the mammalian cell is derived from a cell line.

15. The method of claim 14 wherein the cell line is selected from the group consisting of Rat-1 fibroblasts, COS cells, CHO cells and HEK-293 cells.

16. The method of claim 1 wherein the step of isolating the protein tyrosine phosphatase comprises cell lysis.

17. The method of claim 16 wherein the step of isolating further comprises gel electrophoresis of the protein tyrosine phosphatase.

18. The method of claim 17 wherein the step of isolating further comprises electrophoresis of the protein tyrosine phosphatase in a gel comprising the detectably labeled protein tyrosine phosphatase substrate.

19. The method of claim 16 wherein the step of isolating further comprises detecting the protein tyrosine phosphatase with an antibody that specifically binds to the phosphatase.

20. The method of claim 1 wherein the stimulus increases reactive oxygen species in the sample.

21. The method of claim 1 wherein the stimulus is selected from the group consisting of a cytokine, a growth factor, a hormone, a cell stressor and a peptide.

22. The method of claim 21 wherein the cell stressor is selected from the group consisting of a source of ROS and ultraviolet light.

23. The method of claim 1 wherein the stimulus is selected from the group consisting of PDGF, EGF, bFGF, insulin, GM-CSF, TGF-β1, IL-1, IL-3, IFN-γ, TNF-α, PHA, AT-2, thrombin, thyrotropin, parathyroid hormone, LPA, sphingosine-1-phosphate, serotonin, endothelin, acetylcholine, platelet activating factor, bradykinin and G-CSF.

24. A method for identifying a protein tyrosine phosphatase that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine with a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase;

isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly modified by a PTP active site-binding agent in a cell.

25. The method of claim 24 wherein the step of isolating is performed anaerobically.

26. The method of claim 24 wherein the PTP active site-binding agent is selected from the group consisting of an agent that covalently binds to the PTP active site and an agent that non-covalently binds to the PTP active site.

27. The method of claim 24 wherein the PTP active site-binding agent is selected from the group consisting of a sulfonated compound and a vanadate compound.

28. The method of claim 24 wherein the PTP active site-binding agent covalently and reversibly modifies a sulfhydryl group of a PTP active site invariant cysteine.

29. The method of claim 28 wherein the step of determining comprises reversing a covalent modification of a sulfhydryl group of a PTP active site invariant cysteine.

30. The method of claim 29 wherein the step of reversing comprises contacting the PTP with a reducing agent.

31. The method of claim 30 wherein the reducing agent is selected from the group consisting of dithiothreitol, dithioerythritol, and 2-mercaptoethanol.

32. The method of claim 24 wherein the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is selected from the group consisting of iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog, and N-ethylmaleimide.

33. A method for identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a protein tyrosine phosphatase active site invariant cysteine from modification;

isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

determining, under conditions that reverse the reversible protection of the protein tyrosine phosphatase active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell.

34. The method of claim 33 wherein the step of isolating is performed anaerobically.

35. The method of claim 33 wherein the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is selected from the group consisting of iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog, and N-ethylmaleimide.

36. A method for identifying an agent that alters an inducible biological signaling pathway, comprising:

(a) identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus under conditions and for a time sufficient to induce reversible oxidation of at least one protein tyrosine phosphatase in the cell;

(ii) isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine;

(iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell;

(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises the PTP that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of the PTP;

(c) isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

(d) determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent

relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

37. The method of claim 36 wherein the step of isolating in the method recited in (a) is performed anaerobically.

38. The method of claim 36 wherein the step of isolating recited in (c) is performed anaerobically.

39. A method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell, comprising:

contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2 in the cell;

isolating anaerobically SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell.

40. A method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell, comprising:

contacting a biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell;

isolating anaerobically PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell.

41. A method for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly oxidized in a cell, comprising:

contacting a biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45 in the cell;

isolating anaerobically TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell.

42. A method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine with a biological sample comprising a cell that comprises SHP-2;

isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a SHP-2 active site invariant cysteine, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly modified by a PTP active site-binding agent in a cell.

43. A method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine with a biological sample comprising a cell that comprises PTP1B;

isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a PTP1B active site invariant cysteine, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly modified by a PTP active site-binding agent in a cell.

44. A method for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine with a biological sample comprising a cell that comprises TC45;

isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a TC45 active site invariant cysteine, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly modified by a PTP active site-binding agent in a cell.

45. A method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a SHP-2 active site invariant cysteine from modification;

isolating the SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

determining, under conditions that reverse the reversible protection of the SHP-2 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is a reversibly modified component of an inducible biological signaling pathway in a cell.

46. A method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

contacting a biological sample comprising a cell that comprises PTP1B with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a PTP1B active site invariant cysteine from modification;

isolating the PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

determining, under conditions that reverse the reversible protection of the PTP1B active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is a reversibly modified component of an inducible biological signaling pathway in a cell.

47. A method for identifying a TC45 protein tyrosine phosphatase (TC45) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

contacting a biological sample comprising a cell that comprises TC45 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a TC45 active site invariant cysteine from modification;

isolating the TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

determining, under conditions that reverse the reversible protection of the TC45 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is a reversibly modified component of an inducible biological signaling pathway in a cell.

48. A method for identifying an agent that alters an inducible biological signaling pathway, comprising:

(a) identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2 in the cell;

(ii) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine;

(iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell;

(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises SHP-2 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2;

(c) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

(d) determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2

comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

49. A method for identifying an agent that alters an inducible biological signaling pathway, comprising:

(a) identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell;

(ii) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine;

(iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell;

(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises PTP1B that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B;

(c) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

(d) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

50. A method for identifying an agent that alters an inducible biological signaling pathway, comprising:

(a) identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45 in the cell;

(ii) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine;

(iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein detectable

substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell;

(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises TC45 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45;

(c) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

(d) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM_080422,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

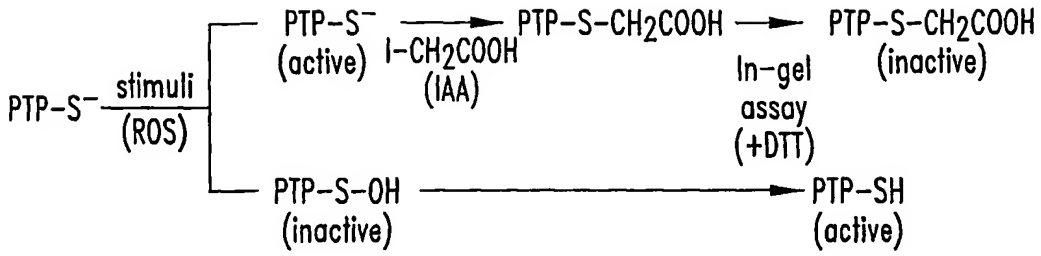



*FIG. 1*

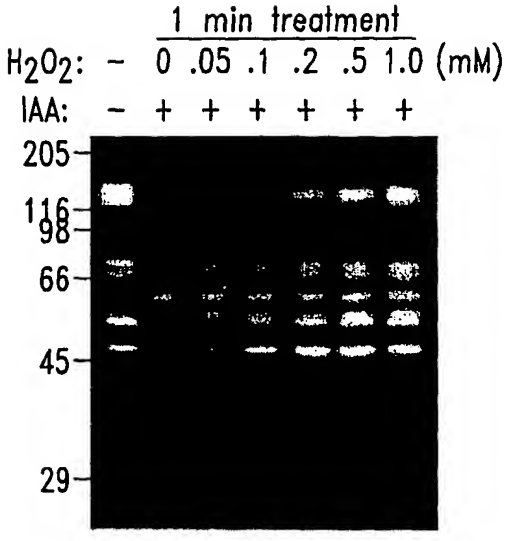



*FIG. 2A*

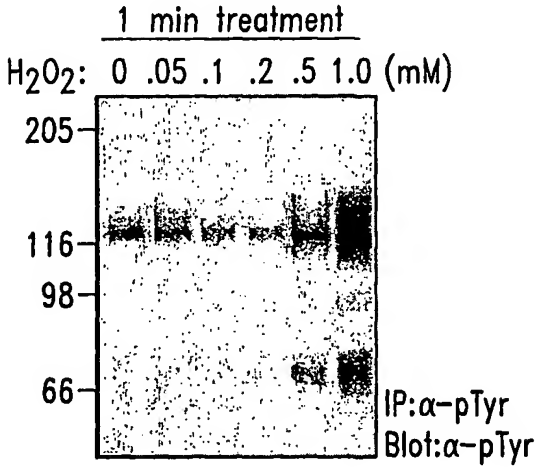



*FIG. 2B*

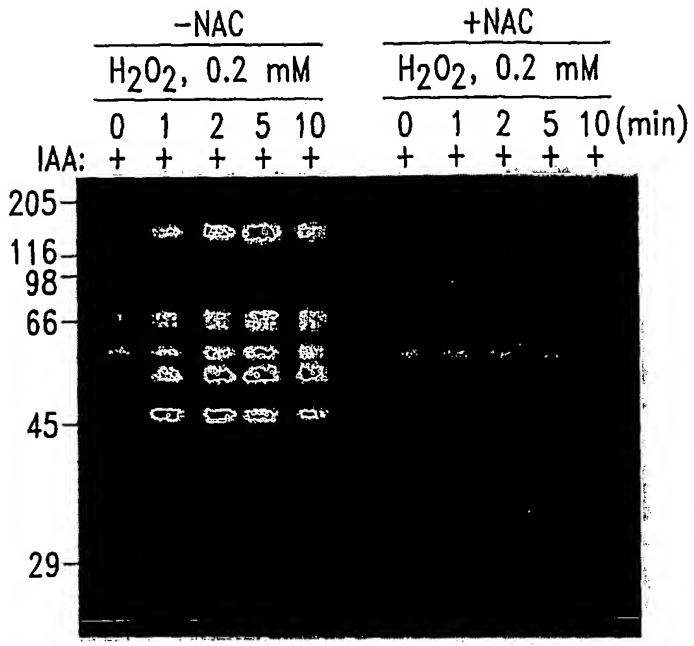



*FIG. 2C*

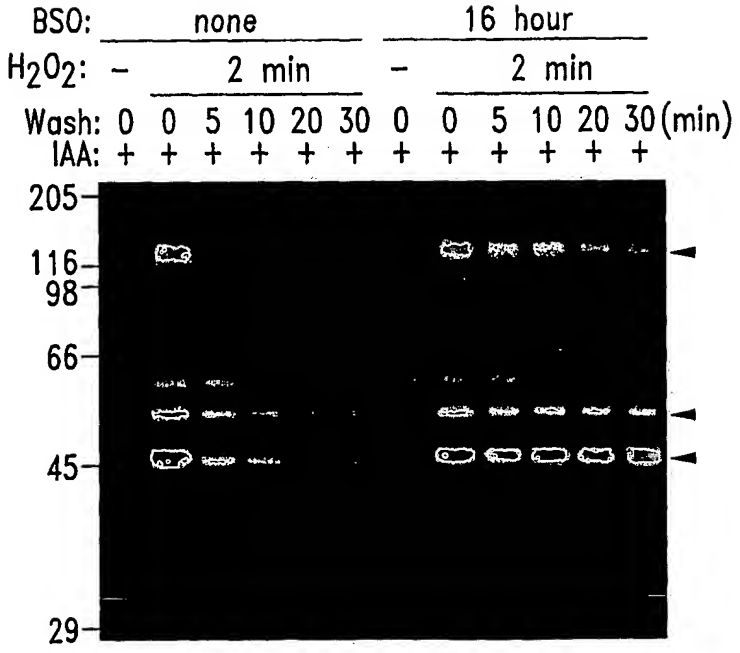



*FIG. 2D*

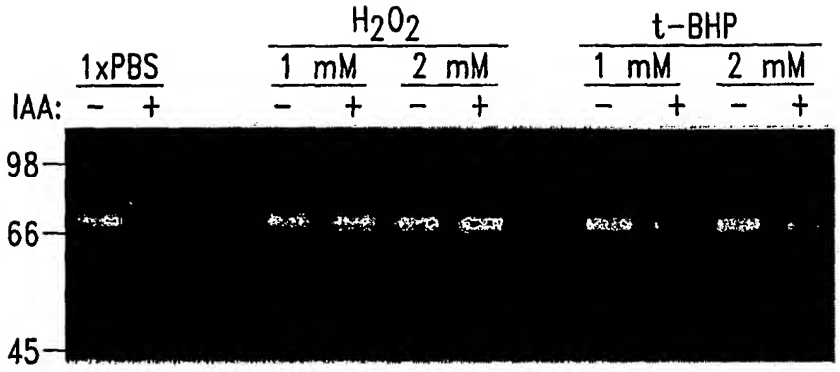



*FIG. 3A*

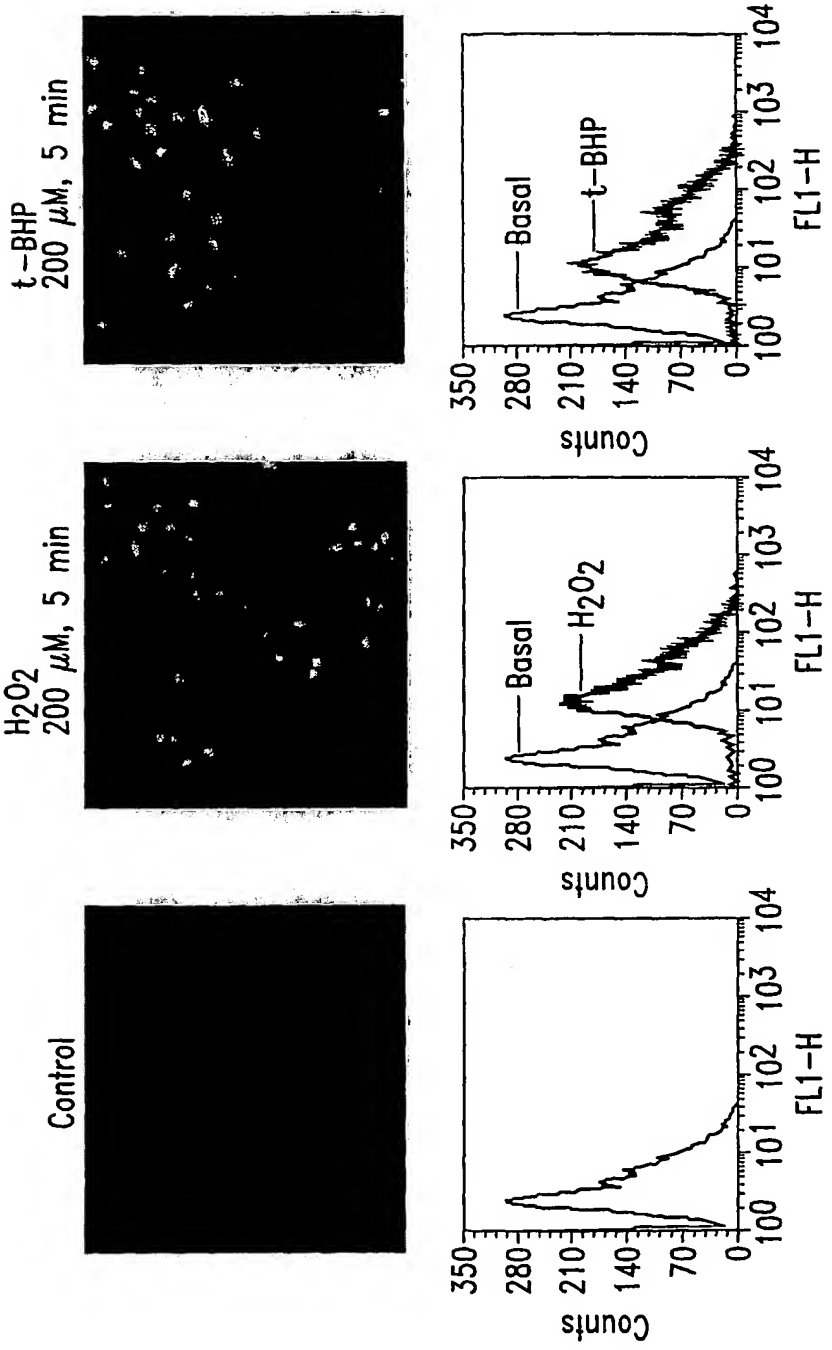



FIG. 3B

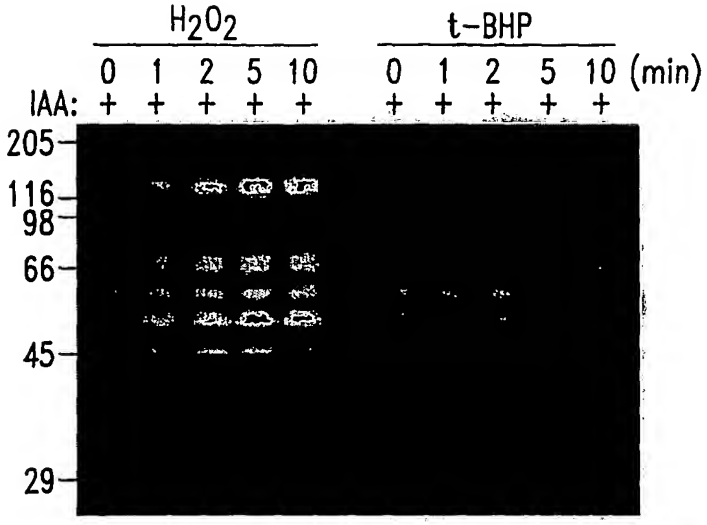



FIG. 3C

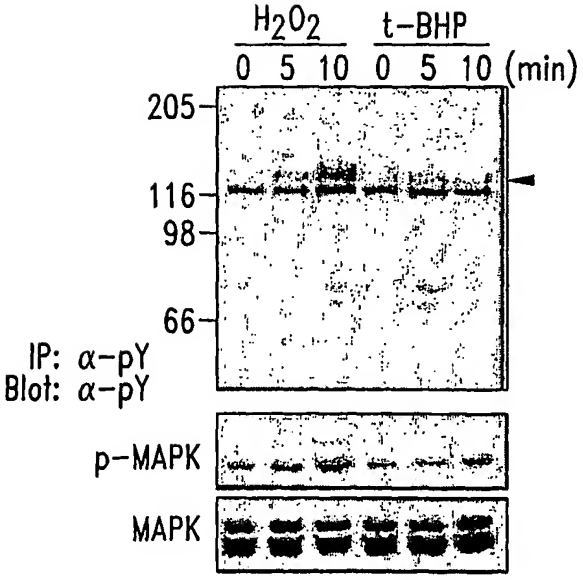



FIG. 3D

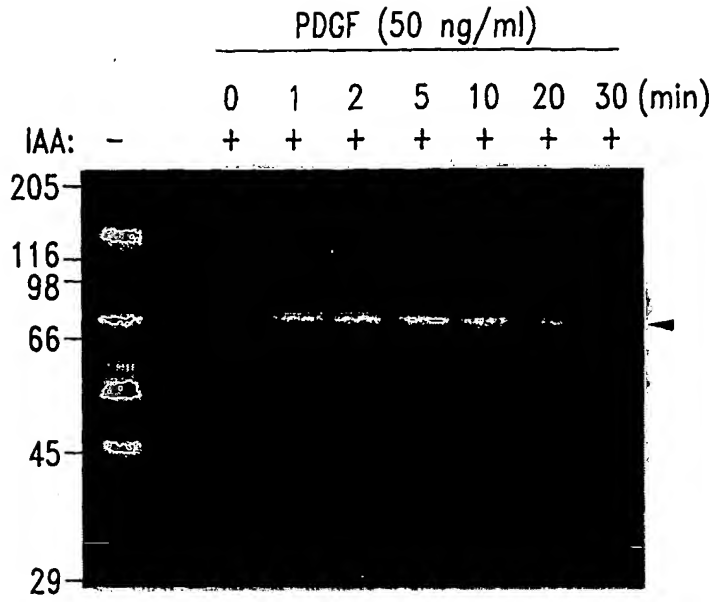



FIG. 4A

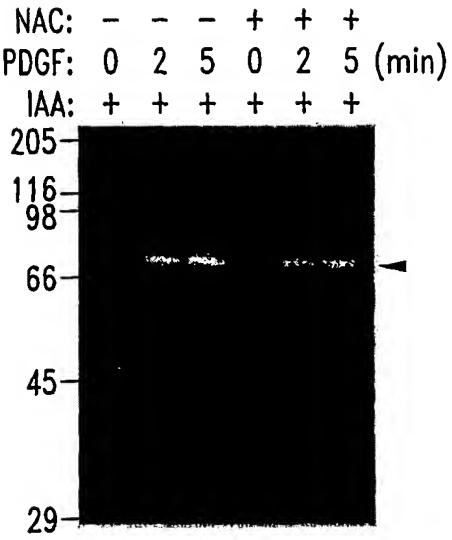



FIG. 4B

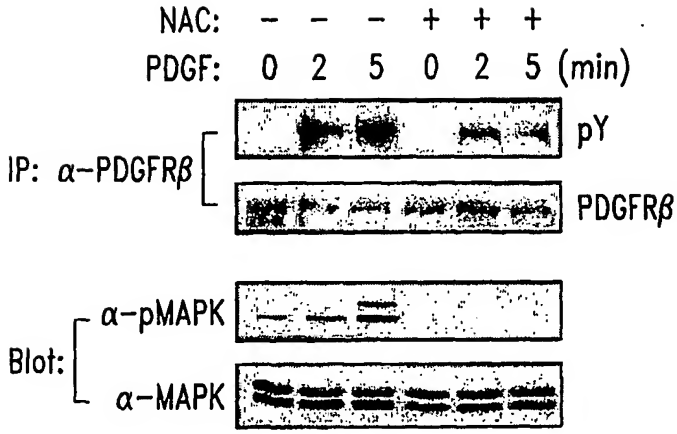



FIG. 4C

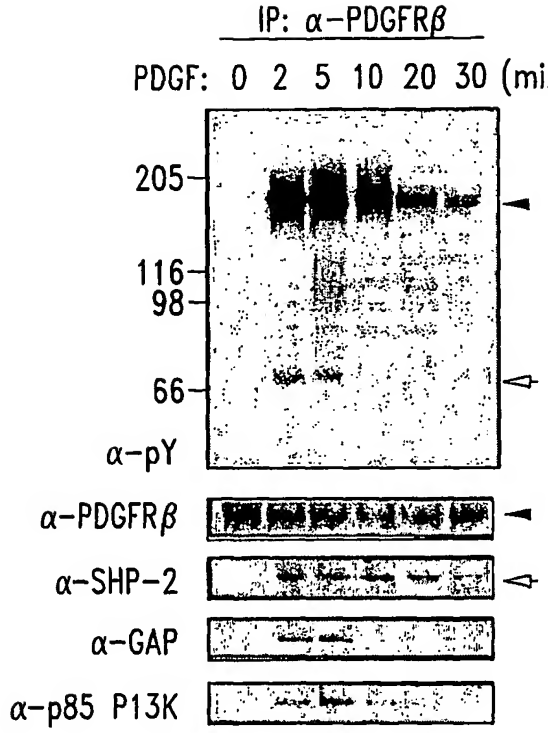



*FIG. 5A*

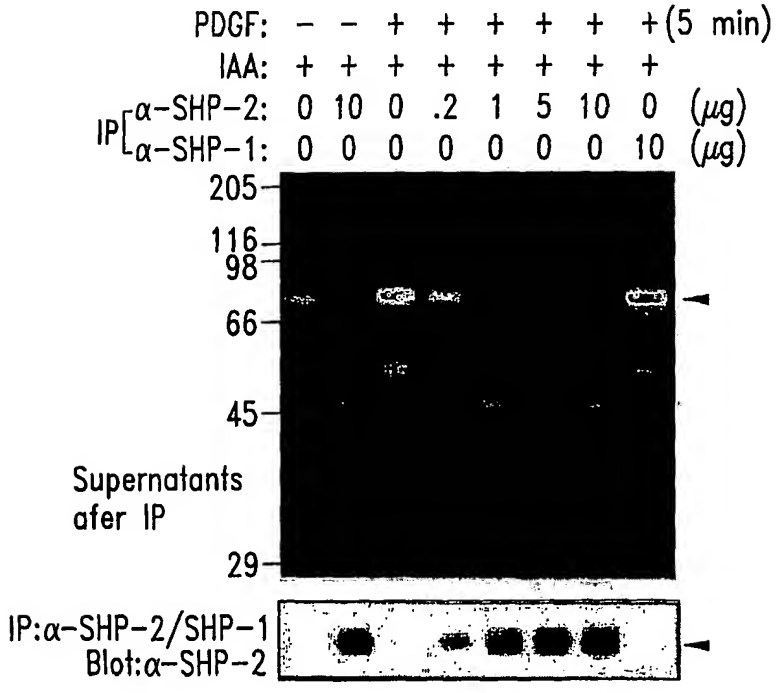



*FIG. 5B*

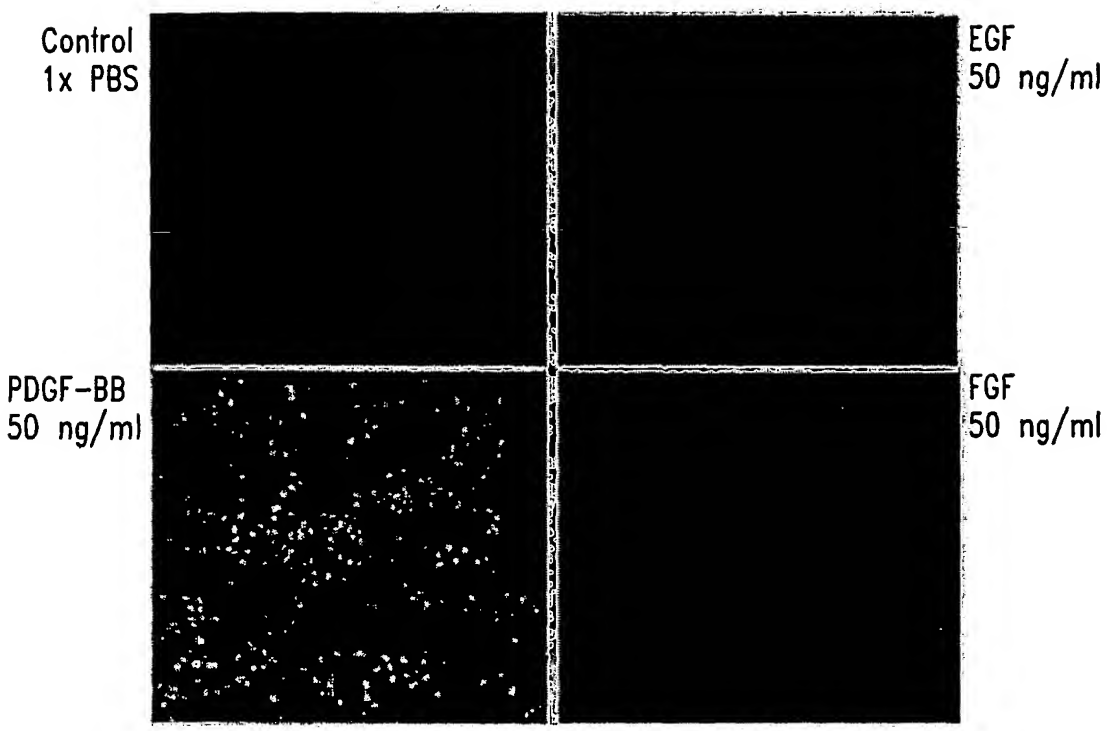



*FIG. 6A*

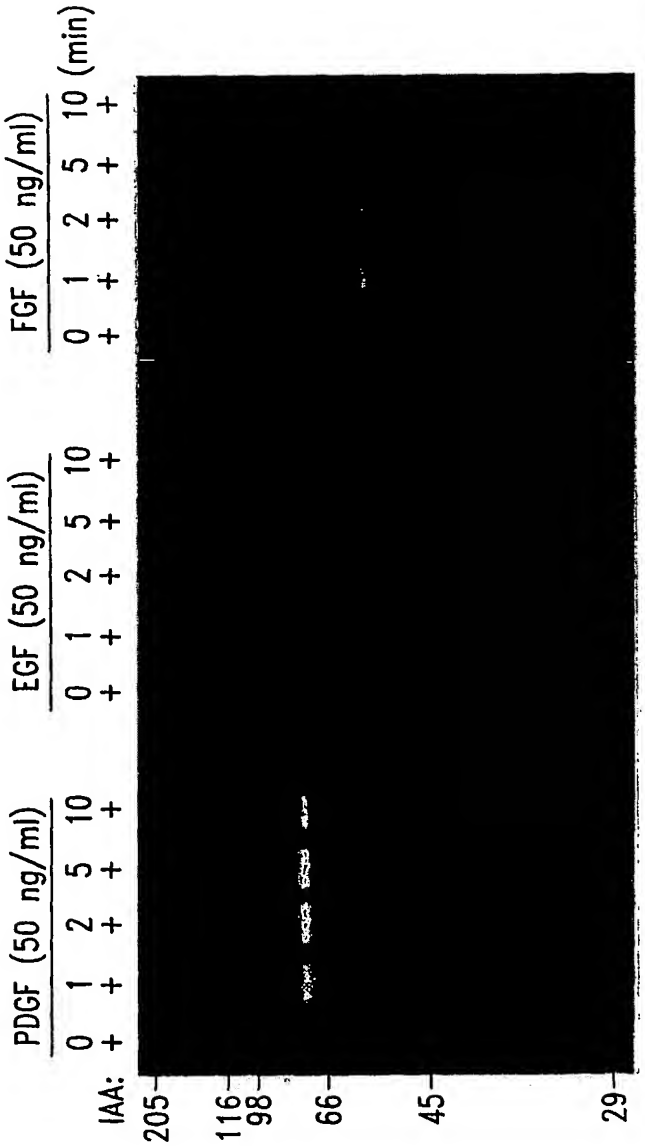



FIG. 6B

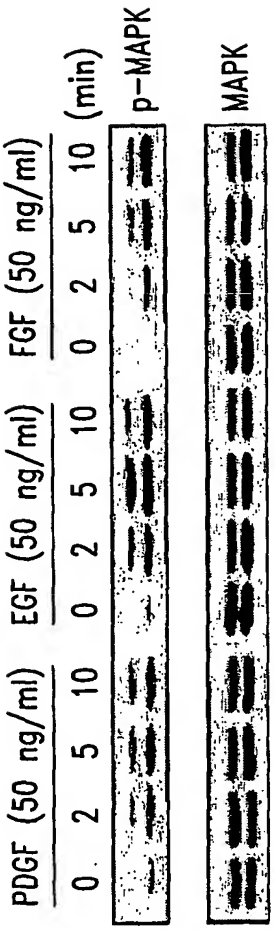



FIG. 6C

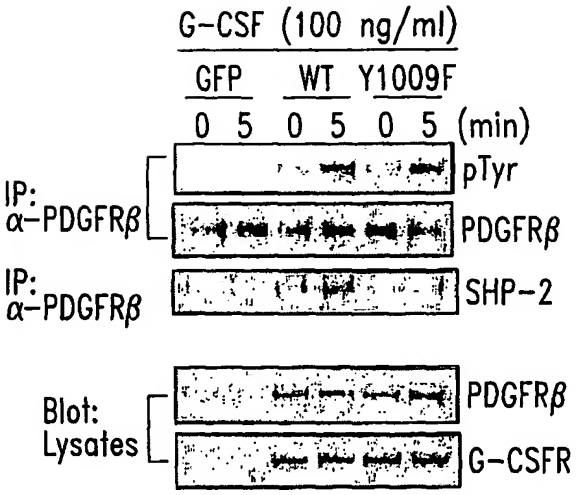



*FIG. 7A*

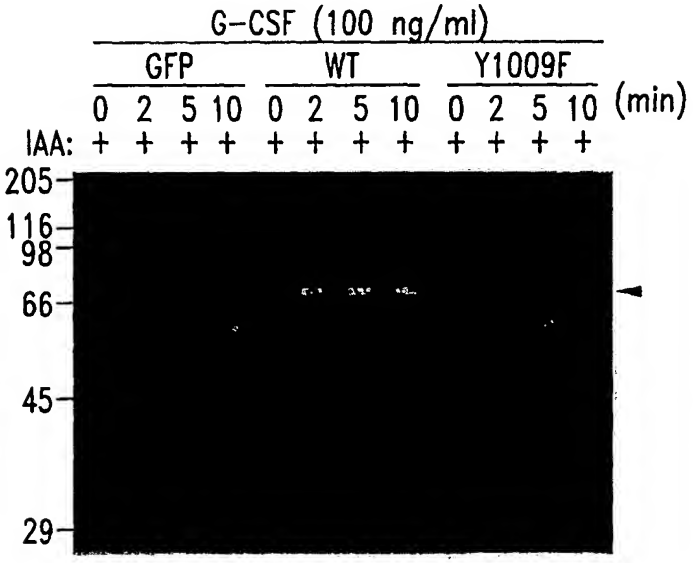



*FIG. 7B*

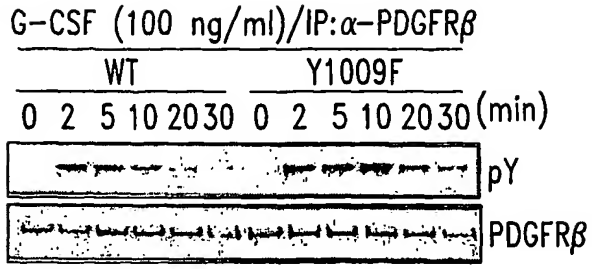



FIG. 7C

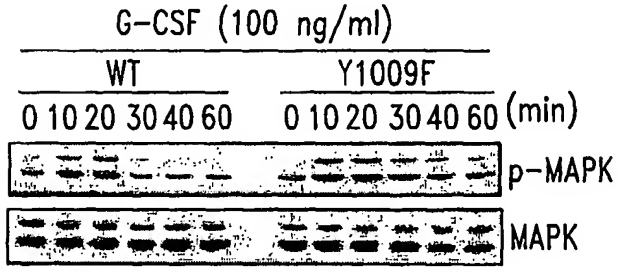



FIG. 7D

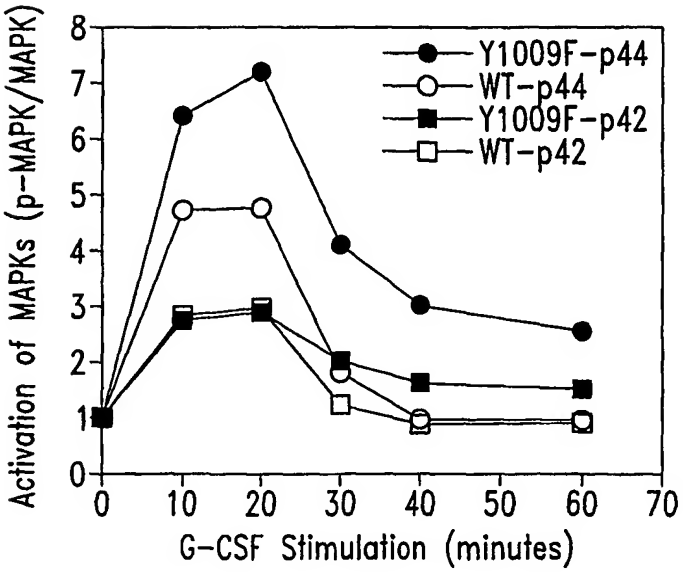



FIG. 7E

Compilation of nonredundant set of 113 vertebrate PTPs

| Name | Subtype | Human ortholog | Full-length name | Synonym(s) | Swiss-Prot | GenBank accession no. |
|---|---|---|---|---|---|---|
| Non-RPTP subtypes | | | | | | |
| hPTP1B | NT1 | | PTP1B | PTP-1, PTP-1B | P18031 | M31724, M33689, |
| mPTP1B | NT1 | PTP1B | PTP1B | PTP-1, HA2, PTP-HA2 | P35821 | U24700, Z23057, M97590, L40595 |
| rPTP1B | NT1 | PTP1B | PTP1B | PTP-1 | P20417 | M33962 |
| cPTP1B | NT1 | PTP1B | PTP1B | | Q13016 | U86410 |
| zPTP1B | NT1 | PTP1B | PTP1B | | | AF097481, AF097482, AF097483 |
| hTCPTP | NT1 | | TC-PTP (T-cell phosphatase) | PTP-2 | P17706 | M25393, M81478, M80737 |
| mTCPTP | NT1 | TCPTP | TC-PTP (T-cell phosphatase) | PTP-2 | Q06180 | S52655, M81477, M80739 |
| rTCPTP | NT1 | TCPTP | TC-PTP (T-cell phosphatase) | PTP-2, PTP-S | P35233 | X58828 |
| hSHP1 | NT2 | | Src homology domain 2-containing PTP1 | SH-PTP1, SHP, HCP, PTP1C | P29350 | M74903, X62055, M77273, M90388, X82817, X82818 |
| mSHP1 | NT2 | SHP1 | Src homology domain 2-containing PTP1 | | P29351 | M68902, M90389, U65953, U65954, U65955 |
| rSHP1 | NT2 | SHP1 | Src homology domain 2-containing PTP1 | | | U77038 |
| hSHP2 | NT2 | | Src homology domain 2-containing PTP2 | SH-PTP2, SH-PTP3, Syp, PTP-2C, PTP1D | Q06124 | D13540, L03535, L07527, X70766, L08807, S78088, S398383 |
| mSHP2 | NT2 | SHP2 | Src homology domain 2-containing PTP2 | SH-PTP2, Syp | P35235 | L08663, D84372 |
| rSHP2 | NT2 | SHP2 | Src homology domain 2-containing PTP2 | PTP-1D | P41499 | U09307, J05963, D83016 |
| cSHP2 | NT2 | SHP2 | Src homology domain 2-containing PTP2 | SH-PTP2, Syp | | U38620 |
| xSHP2 | NT2 | SHP2 | Src homology domain 2-containing PTP2 | | | U15287 |
| hMEG2 | NT3 | | Megakaryocyte-PTP2 | | P43378 | M83738 |
| mMEG2 | NT3 | MEG2 | Megakaryocyte-PTP2 | | | AF013490 |
| xPTPX1 | NT3 | -- | | | | L33098 |
| xPTPX10 | NT3 | -- | | | | L33099 |
| hPEST | NT4 | | Pro, Glu, Ser, Thr-rich PTP | PTP-PEST, PTPG1 | Q05209 | D13380, M93425, S69184 |
| mPEST | NT4 | PEST | Pro, Glu, Ser, Thr-rich PTP | PTPP19 | P35831 | X86781, X63440, S36169 |
| rRKPTP | NT4 | PEST | Rat kidney PTP | | | D38072 |
| hLyPTP | NT4 | | Lymphoid phosphatase | LyP1, LyP2 | | AF001846, AF001847, AF077031, AF150732 |

*FIG. 8A*

| Name | Subtype | Human ortholog | Full-length name | Synonym(s) | Swiss-Prot | GenBank accession no. |
|---|---|---|---|---|---|---|
| mPEP | NT4 | LyPTP | Hematopoietic cell PTP | | P29352 | M90388 |
| hBDP1 | NT4 | | Brain-derived phosphatase 1 | | | X79568 |
| rPTP2D | NT4 | BDP1 | | | | U69673 |
| mPTPK1 | NT4 | BDP1 | | PTPFLP1 (fetal liver phosphatase 1) | | U35124, U52523, U49853 |
| | | | | | | |
| hMEG1 | NT5 | | Megakaryocyte-PTP1 | PTPG1, PTPF36-15 | P29074 | M68941, AAB26477 |
| mPTPtep | NT5 | MEG1 | Testis-enriched phosphatase | PTPMEG | | AF106702 |
| zPTPH1 | NT5 | | | MEG1 | | AF097477, AF097478, AF097479, AF097480 |
| hPTPH1 | NT5 | PTPH1 | | | P26045 | M64572, S39392 |
| | | | | | | |
| mPTPRL10 | NT6 | | PTPD1 | | Q62136 | D37801, D83072 |
| rPTP2E | NT6 | PTPD1 | PTPD1 | | Q62728 | U17971, U18293 |
| hPTPD1 | NT6 | PTPD1 | PTPD1 | | Q16825 | X79510 |
| hPTPD2 | NT6 | | PTPD2 | PEZ (phosphatase ezrin-like) | Q15678 | X82676 |
| mPTP36 | NT6 | PTPD2 | PTPD2 | | Q62130 | D31842 |
| | | | | | | |
| hPTPBAS | NT7 | | FAS-associated PTP1 | BAS, PTP1E, PTPE1, FAP-1, PTPL1, CD95 | Q12923 | X80289, U12128, D21209, D21210, D21211, U81561, X79676 |
| mPTPBL | NT7 | PTPBAS | | DPZPTP, PTPRIP | | D28529, Z32740, D83966 |
| bPTPBA14 | NT7 | PTPBAS | | | | U20807 |
| | | | | | | |
| hPTPTyp | NT8 | | Testis-specific tyrosine phosphatase | Typ | | AL050040 |
| mPTPTyp | NT8 | PTPTyp | Testis-specific tyrosine phosphatase | Typ | | D64141 |

*FIG. 8B*

| Name | Subtype | Human ortholog | Full-length name | Synonym(s) | Swiss-Prot | GenBank accession no. |
|---|---|---|---|---|---|---|
| hHDPTP | NT9 | | His domain-containing PTP | HD-PTP, PTPTD14 | | T14756, AB025194, AB040904, AL110210, AF169350 |
| rPTPTD14 | NT9 | HDPTP | | | | AF077000 |
| *RPTP subtypes* | | | | | | |
| hCD45 | R1/R6 | | Cluster of differentiation 45 | Leukocyte common antigen (LCA), T200, PTPRC | P08575 | Y00638, Y00062 |
| mCD45 | R1/R6 | CD45 | Cluster of differentiation 45 | LCA, T200, Ly5 | P06800 | M14342, M92933, M33482 |
| rCD45 | R1/R6 | CD45 | Cluster of differentiation 45 | Leukocyte common antigen | P04157 | M10072, Y00065, M25820, M25821, M25822, M25823, K03039 |
| cPTPlambda | R1/R6 | CD45 | PTPlambda | | | L13285, Z21960 |
| xCD45 | R1/R6 | CD45 | Cluster of differentiation 45 | | | AF024438 |
| | | | | | | |
| hPTPlambda | R2A | | RPTPlambda | PCP2, PTPomicron, PTPfmi, PTPpi, PTPi, PTPRO | Q92729 | U60289, X97198, U73727, U71075, X95712,AL049570 |
| mPTPlambda | R2A | PTPλ | RPTPlambda | PTPftp1, PTPpsi | | U55057, D88187 |
| rPTPpsi | R2A | PTP1 | RPTPpsi | | | U66566 |
| hPTPkappa | R2A | | RPTPkappa | | Q15262 | L77886, Z70660 |
| mPTkappa | R2A | PTPκ | RPTPkappa | | P35822 | L10106 |
| hPTPmu | R2A | | RPTPmu | | P28827 | X58288 |
| mPTPmu | R2A | PTPm | TPTPmu | | P28828 | X58287 |
| hPTPrho | R2A | | RPTPrho | | | AF043644, AL024473, AL022239, Z93942 |
| mPTPrho | R2A | PTPr | RPTPrho | | | AF152556 |
| xPTPrho | R2A | PTPr | RPTPrho | | | AF173857 |
| | | | | | | |
| hLAR | R2B | | LCA-related PTP | PTP-LAR | P10586 | Y00815 |
| mLAR | R2B | LAR | LCA-related PTP | PTP-LAR | | Z37988 |
| rLAR | R2B | LAR | LCA-related PTP | PTP-LAR | | L11586, U00477, X83546, X83505 |
| xLAR | R2B | LAR | LCA-related PTP | PTP-LAR | | AF197945 |
| hPTPdelta | R2B | | RPTPdelta | | P23468 | X54133, L38929 |
| mPTPdelta | R2B | PTPδ | RPTPdelta | | | D13903 |
| cLAR | R2B | PTPδ | | CRYPalpha | | L32780 |
| xPTPdelta | R2B | PTPδ | RPTPdelta | | | AF197944 |
| hPTPsigma | R2B | | RPTPsigma | | | U35234, U40317, U41725, AC005788, S78080, S78086 |

*FIG. 8C*

| Name | Subtype | Human ortholog | Full-length name | Synonym(s) | Swiss-Prot | GenBank accession no. |
|---|---|---|---|---|---|---|
| rPTPsigma | R2B | PTPσ | RPTPsigma | LAR-PTP2, PTP-PS, PTP-P1 | | L11587, AF073999 |
| mPTPNU3 | R2B | PTPσ | | PTPsigma, PTPT9a, PTPT9b | | X82288, D28530, D28531 |
| xCRYPalpha | R2B | PTPσ | | | | AF198450 |
| | | | | | | |
| hPTPS31 | R3 | | | | | I32038, I32036, I32037, I32035, I32039 |
| rPTPGMC | R3 | PTPS31 | Glomerular mesangial cell receptor | PTPRQ, PTPGMC1 | | AF063249 |
| hGLEPP1 | R3 | | Glomerular epithelial protein 1 | PTPU2, PTProt | | U20489, Z48541 |
| mPTPphi | R3 | GLEPP1 | | PTP-BK, PTP-ro, mGLEPP1 | | U37465, U37466, U37467, AF295638 |
| rPTPBEM1 | R3 | GLEPP1 | Brain-enriched membrane-associated PTP1 | PTPD30, BSM-1 | | D45412, U28938 |
| rabPTPoc | R3 | GLEPP1 | Osteoclastic PTP | | | U32587 |
| cPTPcryp2 | R3 | GLEPP1 | | CRYP-2 | | U65891 |
| hPTPbeta | R3 | | RPTPβ | | P23467 | X54131 |
| mPTPbeta | R3 | PTPβ | | Vascular endothelial PTP (VE-PTP) | | X58289, AF157628 |
| hDEP1 | R3 | | Density-enhanced PTP | PTPeta, CD148, F-36-12 | Q12913 | U10886, D37781, AAB26475 |
| mPTPBYP | R3 | DEP1 | RPTPbeta-like PTP | PTPeta | Q64455 | D45212 |
| rDEP1 | R3 | DEP1 | Density enhanced PTP | Vascular PTP-1 | | U40790 |
| hSAP1 | R3 | | Stomach cancer-associated PTP | hPTPH | | D15049, AAF91411 |
| rPTPBEM2 | R3 | SAP1 | Brain-enriched membrane-associated PTP2 | | | D45413 |
| mPTPesp | R3 | -- | Embryonic stem cell PTP | OST-PTP | P70289 | U36488, AF300701 |
| rOSTPTP | R3 | -- | Osteotesticular PTP | | Q64612 | L36884 |
| | | | | | | |
| hPTPalpha | R4 | | RPTPalpha | | P18433 | M34668, X54130, X54890, X53364 |
| mPTPalpha | R4 | PTPα | RPTPalpha | LCA-related PTP | P18052 | M36033, M33671, M36034 |
| rPTPalpha | R4 | PTPα | RPTPalpha | | Q03348 | L01702 |
| cPTPalpha | R4 | PTPα | RPTPalpha | | | Z32749, L22437, |
| xPTPalpha | R4 | PTPα | RPTPalpha | | | U09135 |
| hPTPepsilon | R4 | | RPTPepsilon | | P23469 | X54134 |
| mPTPepsilon | R4 | PTPε | RPTPepsilon | | P49446 | U35368, U36758, D83484, U62387, U40280 |
| rPTPepsilon | R4 | PTPε | RPTPepsilon | | | D78610, D78613 |

*FIG. 8D*

| Name | Subtype | Human ortholog | Full-length name | Synonym(s) | Swiss-Prot | GenBank accession no. |
|---|---|---|---|---|---|---|
| hPTPgamma | R5 | | RPTPgamma | | P23470 | L09247, X54132 |
| mPTPgamma | R5 | PTPγ | RPTPgamma | | Q05909 | L09562 |
| cPTPgamma | R5 | PTPγ | RPTPgamma | | Q98936 | U38349 |
| cPTPzeta | R5 | | RPTPzeta | | | L27625 |
| hPTPzeta | R5 | PTPζ | RPTPzeta | | P23471 | M93426, X54135, U88967 |
| rPTPzeta | R5 | PTPζ | RPTPzeta | | Q62656 | U09357 |
| | | | | | | |
| hPCPTP1 | R7 | | PC12-derived PTP | PTPCh1g, PTPCOM1, hCh1PTPα, PTPEC | | D64053, U77916, U77917, U42361, X82635, Z79693 |
| rPCPTP1 | R7 | PCPTP | PC 12-derived PTP | PC12-PTP1, CBPTP | | D38292, D64050, U14914 |
| mPTPSL | R7 | PCPTP | | PTPBR7, PTP-SL, PC 12-PTP1 | | Z30313, AF041866, D31898 |
| hSTEP | R7 | | Striatum-enriched phosphatase | | P54829 | U27831 |
| mSTEP61 | R7 | STEP | Striatum-enriched phosphatase | | P54830 | U28217, S80329, U28216 |
| rSTEP | R7 | STEP | Striatum-enriched phosphatase | | P35234 | S49400 |
| hHePTP | R7 | | Hematopoetic PTP | Leucocyte PTP | P35236 | M64322, D11327 |
| rLCPTP | R7 | HePTP | Leukocyte PTP | Hematopoetic PTP | P49445 | U28356 |
| | | | | | | |
| IA2 Receptor-Like subtype | | | | | | |
| hPTPIA2 | R8 | | Islet cell antigen | Islet cell antigen, ICA- 512 | Q16849 | L18983, Z48226, X62899 |
| mPTPIA2 | R8 | IA2 | Islet cell antigen | PTP35 | Q60673 | U11812, X74438 |
| rPTPIA2 | R8 | IA2 | Islet cell antigen | BEM-3, PTPN, ICA105, PTPLP | Q63259 | D45414, X92563, D38222, U40652 |
| bPTPIA2 | R8 | IA2 | Islet cell antigen | ICA512 | P56722 | AF075170 |
| hPTPIA2beta | R8 | | PTP-IA-2beta | IAR, RPTPX | Q92932 | U65065, AF007555, L76258, U81561, AB002385 |
| mPTPNP | R8 | IA2β | Nervous system and pancreatic PTP | IA2beta, RPTPX, PTPNP-2 | P80560 | U57345 |
| macPTPIA2beta | R8 | IA2β | | IA2beta | O02695 | U91574 |
| rPTPNE6 | R8 | IA2β | | IA2beta, phogrin | Q63475 | U73458, Z50735 |

*FIG. 8E*

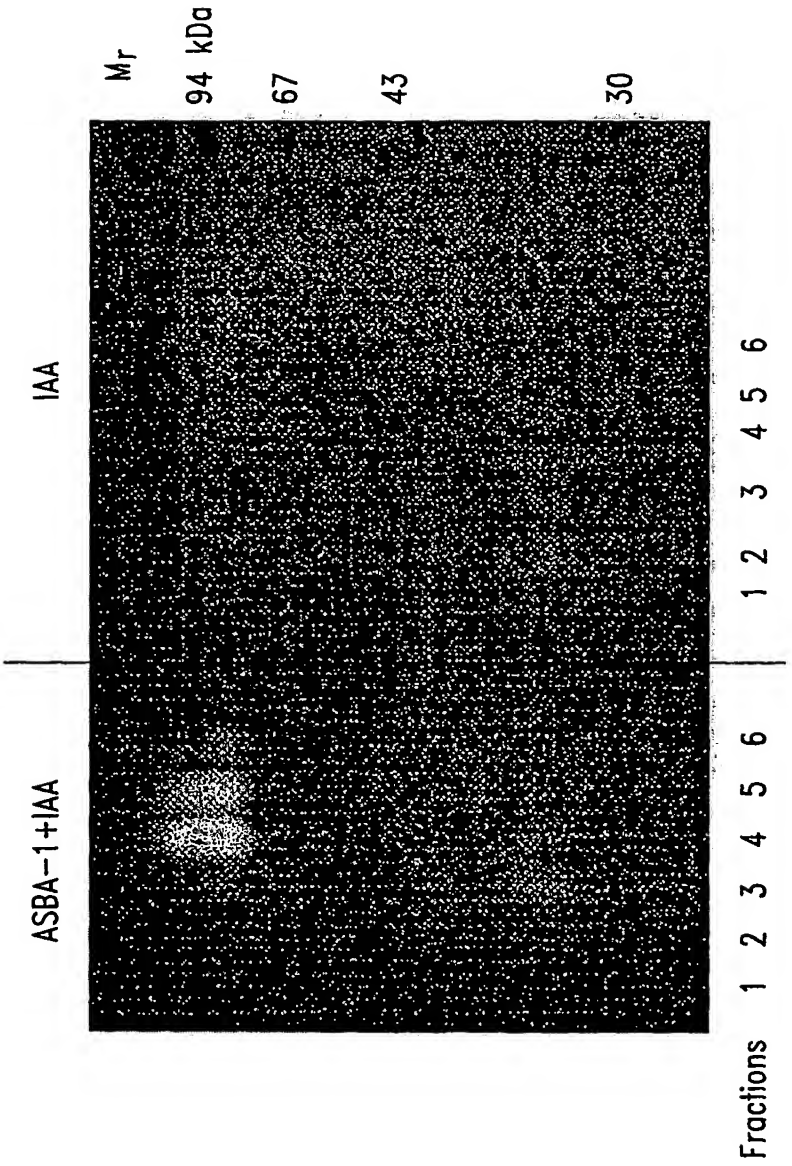



FIG. 9

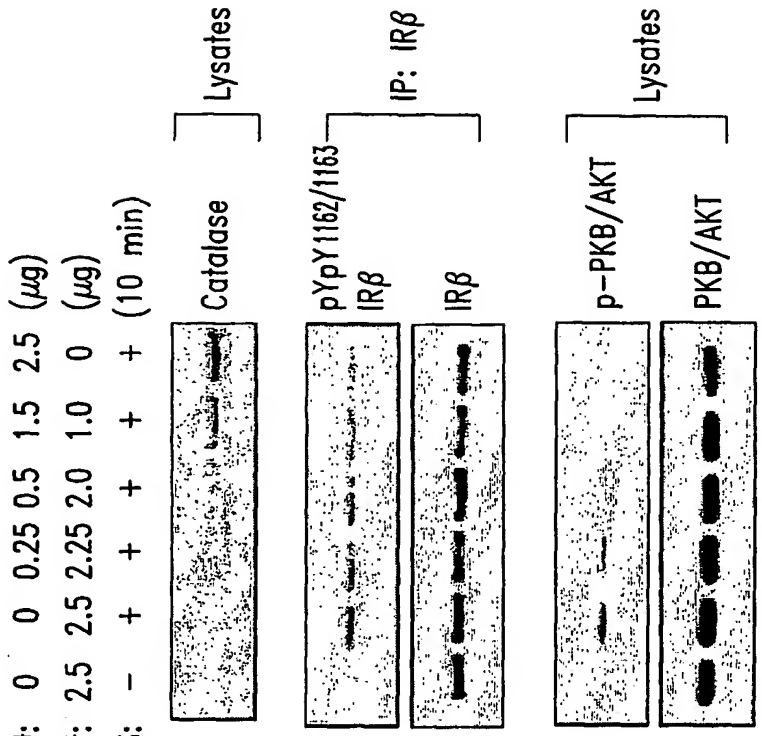



FIG. 10B

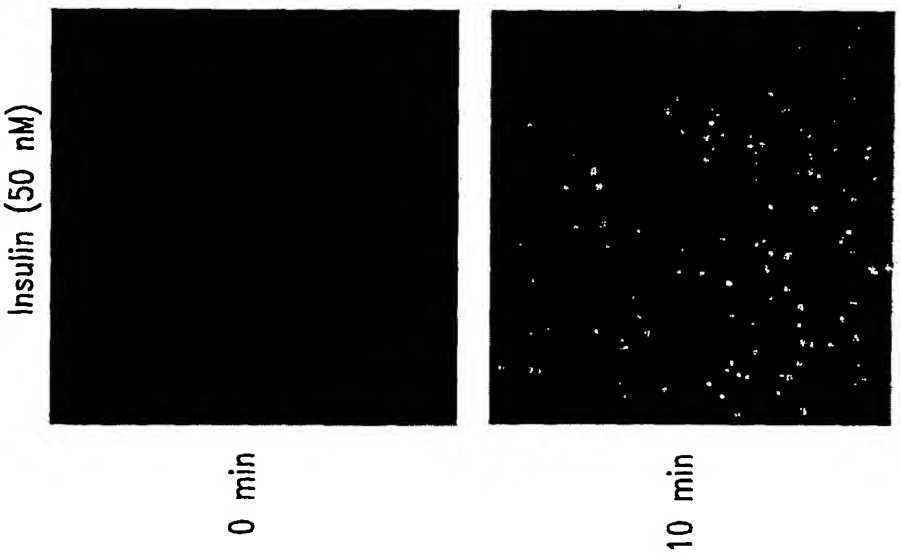



FIG. 10A

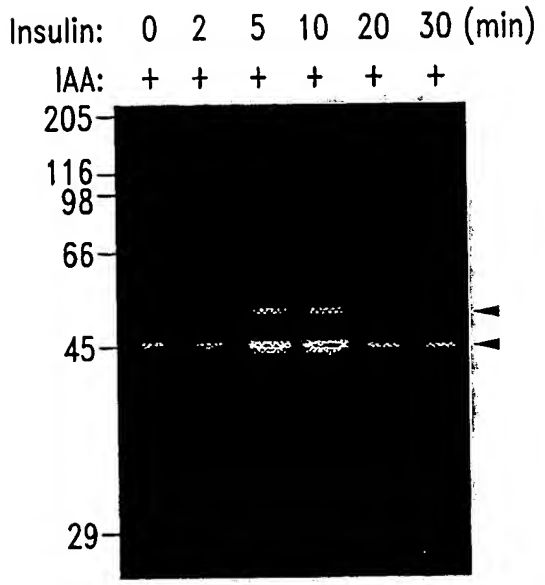



FIG. 11A

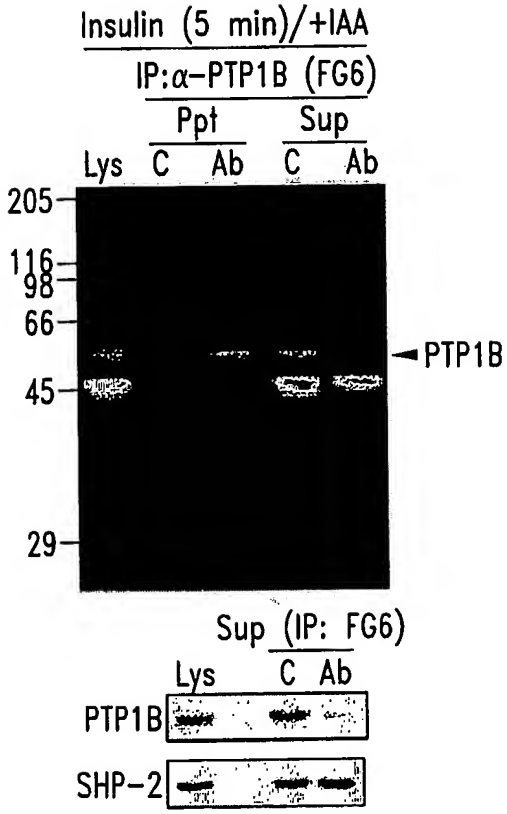



FIG. 11B

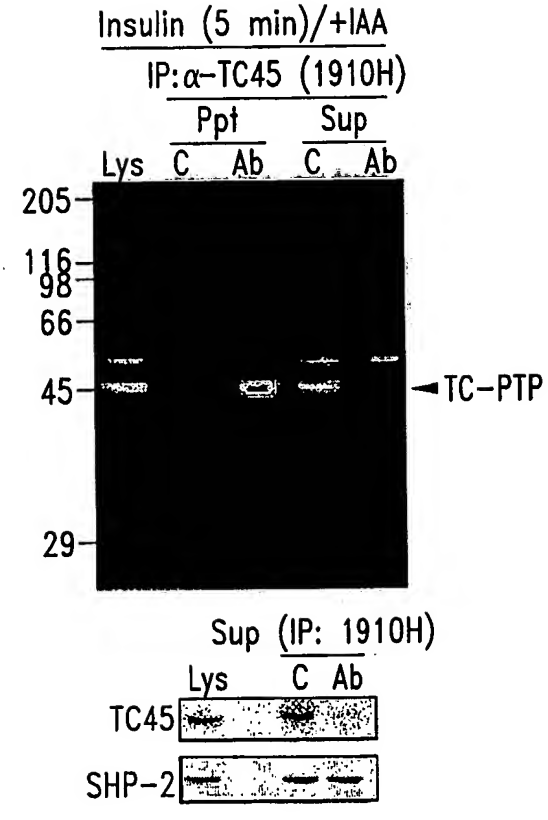



FIG. 11C

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Cool, Deborah E.

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Asn Gly Lys Cys Arg Glu Phe Phe Pro Asn His Gln Trp Val Lys Glu
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Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
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Pro Leu Asn Ala Ala Pro Tyr Gly Ile Glu Ser Met Ser Gln Asp Thr
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Glu Val Arg Ser Arg Val Val Gly Gly Ser Leu Arg Gly Ala Gln Ala
    370                 375                 380
Ala Ser Pro Ala Lys Gly Glu Pro Ser Leu Pro Glu Lys Asp Glu Asp
385                 390                 395                 400
His Ala Leu Ser Tyr Trp Lys Pro Phe Leu Val Asn Met Cys Val Ala
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<210> 3
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<213> Homo sapiens

<400> 3

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<210> 4
<211> 435
<212> PRT
<213> Homo sapiens

<400> 4

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| 1 | | | | 5 | | | | 10 | | | | | | 15 | |
| Ala | Ala | Ile | Tyr | Gln | Asp | Ile | Arg | His | Glu | Ala | Ser | Asp | Phe | Pro | Cys |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Arg | Val | Ala | Lys | Leu | Pro | Lys | Asn | Lys | Asn | Arg | Asn | Arg | Tyr | Arg | Asp |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Val | Ser | Pro | Phe | Asp | His | Ser | Arg | Ile | Lys | Leu | His | Gln | Glu | Asp | Asn |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Asp | Tyr | Ile | Asn | Ala | Ser | Leu | Ile | Lys | Met | Glu | Glu | Ala | Gln | Arg | Ser |
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| Tyr | Ile | Leu | Thr | Gln | Gly | Pro | Leu | Pro | Asn | Thr | Cys | Gly | His | Phe | Trp |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Glu | Met | Val | Trp | Glu | Gln | Lys | Ser | Arg | Gly | Val | Val | Met | Leu | Asn | Arg |
| | | | 100 | | | | | 105 | | | | | 110 | | |
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| | | 115 | | | | | 120 | | | | | 125 | | | |

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Glu Glu Lys Glu Met Ile Phe Glu Asp Thr Asn Leu Lys Leu Thr Leu
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Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr
                165                 170                 175
Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
            180                 185                 190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His
        195                 200                 205
Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
    210                 215                 220
Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225                 230                 235                 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Lys Phe
                245                 250                 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
            260                 265                 270
Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
        275                 280                 285
Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
    290                 295                 300
His Ile Pro Pro Pro Pro Arg Pro Pro Lys Arg Ile Leu Glu Pro His
305                 310                 315                 320
Asn Gly Lys Cys Arg Glu Phe Phe Pro Asn His Gln Trp Val Lys Glu
                325                 330                 335
Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
            340                 345                 350
Pro Leu Asn Ala Ala Pro Tyr Gly Ile Glu Ser Met Ser Gln Asp Thr
        355                 360                 365
Glu Val Arg Ser Arg Val Val Gly Gly Ser Leu Arg Gly Ala Gln Ala
    370                 375                 380
Ala Ser Pro Ala Lys Gly Glu Pro Ser Leu Pro Glu Lys Asp Glu Asp
385                 390                 395                 400
His Ala Leu Ser Tyr Trp Lys Pro Phe Leu Val Asn Met Cys Val Ala
                405                 410                 415
Thr Val Leu Thr Ala Gly Ala Tyr Leu Cys Tyr Arg Phe Leu Phe Asn
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Ser Asn Thr
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<210> 5
<211> 2346
<212> DNA
<213> Mus musculus

<400> 5

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<210> 6
<211> 432
<212> PRT
<213> Mus musculus

<400> 6

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Lys Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
        35                  40                  45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
    50                  55                  60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65                  70                  75                  80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
                85                  90                  95
Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
            100                 105                 110
Ile Met Glu Lys Gly Ser Leu Lys Cys Ala Gln Tyr Trp Pro Gln Gln
        115                 120                 125
Glu Glu Lys Glu Met Val Phe Asp Asp Thr Gly Leu Lys Leu Thr Leu
    130                 135                 140
Ile Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu
145                 150                 155                 160
Glu Asn Leu Thr Thr Lys Glu Thr Arg Glu Ile Leu His Phe His Tyr
```

```
                165                 170                 175
Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
            180                 185                 190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Leu Glu His
        195                 200                 205
Gly Pro Ile Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
    210                 215                 220
Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225                 230                 235                 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Arg Phe
                245                 250                 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
            260                 265                 270
Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
        275                 280                 285
Asp Gln Trp Lys Glu Leu Ser Arg Glu Asp Leu Asp Leu Pro Pro Glu
    290                 295                 300
His Val Pro Pro Pro Pro Arg Pro Pro Lys Arg Thr Leu Glu Pro His
305                 310                 315                 320
Asn Gly Lys Cys Lys Glu Leu Phe Ser Ser His Gln Trp Val Ser Glu
                325                 330                 335
Glu Thr Cys Gly Asp Glu Asp Ser Leu Ala Arg Glu Glu Gly Arg Ala
            340                 345                 350
Gln Ser Ser Ala Met His Ser Val Ser Ser Met Ser Pro Asp Thr Glu
        355                 360                 365
Val Arg Arg Arg Met Val Gly Gly Gly Leu Gln Ser Ala Gln Ala Ser
    370                 375                 380
Val Pro Thr Glu Glu Glu Leu Ser Ser Thr Glu Glu Glu His Lys Ala
385                 390                 395                 400
His Trp Pro Ser His Trp Lys Pro Phe Leu Val Asn Val Cys Met Ala
                405                 410                 415
Thr Leu Leu Ala Thr Gly Ala Tyr Leu Cys Tyr Arg Val Cys Phe His
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<210> 7
<211> 3247
<212> DNA
<213> Homo sapiens

<400> 7

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<210> 8
<211> 435
<212> PRT
<213> Homo sapiens

<400> 8

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            20                  25                  30
Arg Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
        35                  40                  45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
    50                  55                  60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65                  70                  75                  80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
                85                  90                  95
Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
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            100                 105                 110
Val Met Glu Lys Gly Ser Leu Lys Cys Ala Gln Tyr Trp Pro Gln Lys
        115                 120                 125
Glu Glu Lys Glu Met Ile Phe Glu Asp Thr Asn Leu Lys Leu Thr Leu
    130                 135                 140
Ile Ser Glu Asp Ile Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu
145                 150                 155                 160
Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr
                165                 170                 175
Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
            180                 185                 190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His
        195                 200                 205
Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
    210                 215                 220
Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225                 230                 235                 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Lys Phe
                245                 250                 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
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Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
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Pro Leu Asn Ala Ala Pro Tyr Gly Ile Glu Ser Met Ser Gln Asp Thr
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Glu Val Arg Ser Arg Val Val Gly Gly Ser Leu Arg Gly Ala Gln Ala
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Ala Ser Pro Ala Lys Gly Glu Pro Ser Leu Pro Glu Lys Asp Glu Asp
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His Ala Leu Ser Tyr Trp Lys Pro Phe Leu Val Asn Met Cys Val Ala
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<212> PRT
<213> Homo sapiens

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Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65                  70                  75                  80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
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Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
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Val Met Glu Lys Gly Ser Leu Lys Cys Ala Gln Tyr Trp Pro Gln Lys
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Glu Glu Lys Glu Met Ile Phe Glu Asp Thr Asn Leu Lys Leu Thr Leu
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Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr
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Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
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Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
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Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
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Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
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Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
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Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
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His Ile Pro Pro Pro Pro Arg Pro Pro Lys Arg Ile Leu Glu Pro His
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Asn Gly Lys Cys Arg Glu Phe Phe Pro Asn His Gln Trp Val Lys Glu
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Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
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<213> Rattus norvegicus

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Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
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Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
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Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
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Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
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145 150 155 160
Glu Asn Leu Ala Thr Gln Glu Ala Arg Glu Ile Leu His Phe His Tyr
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Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
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Gly Pro Ile Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
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Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225 230 235 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Arg Phe
245 250 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
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Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
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Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
290 295 300

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Glu Ser Cys Glu Asp Glu Asp Ile Leu Ala Arg Glu Glu Ser Arg Ala
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Pro Ser Ile Ala Val His Ser Met Ser Ser Met Ser Gln Asp Thr Glu
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Val Arg Lys Arg Met Val Gly Gly Gly Leu Gln Ser Ala Gln Ala Ser
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Val Pro Thr Glu Glu Glu Leu Ser Pro Thr Glu Glu Glu Gln Lys Ala
385                 390                 395                 400
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<211> 2229
<212> DNA
<213> Mus musculus

<400> 13

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<212> PRT
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    50                  55                  60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
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Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
            180                 185                 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
        195                 200                 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
    210                 215                 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
        275                 280                 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
                325                 330                 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
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    370                 375                 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Ala Leu Leu Gln Gly Asn Thr Glu
                405                 410                 415
Arg Thr Val Trp Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val
            420                 425                 430
Pro Ser Asp Pro Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His
        435                 440                 445
Lys Gln Glu Ser Ile Val Asp Ala Gly Pro Val Val Val His Cys Ser
    450                 455                 460
Ala Gly Ile Gly Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile
465                 470                 475                 480
Asp Ile Ile Arg Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys
                485                 490                 495
Thr Ile Gln Met Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu
            500                 505                 510
Ala Gln Tyr Arg Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr
        515                 520                 525
Leu Gln Arg Arg Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His
    530                 535                 540
Glu Tyr Thr Asn Ile Lys Tyr Ser Leu Val Asp Gln Thr Ser Gly Asp
545                 550                 555                 560
Gln Ser Pro Leu Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met
                565                 570                 575
Arg Glu Asp Ser Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln
            580                 585                 590
Gln Arg Ser Phe Arg
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<210> 15
<211> 2236
<212> DNA
<213> Rattus norvegicus

<400> 15

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cgggctcccg agcggggcct cactcggccc cctccatgtg acggcgcctc gtggagcctg 60
agtgagcagc gggtccgtgc ggagccggag gcgggaggaa catgacatcc cggagatggt 120
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gaaatggagc cgttacccac atcaagattc agaacactgg ggactactat gacctctatg 300
gcggggaaaa gtttgccacc ttgcctgaac tggtccagta ttacatggag catcacgggc 360
agctgaaaga gaagaatgga gatgttattg agctcaagta cccactgaac tgtgcagacc 420
ctacctctga aaggtggttc cacggtcact tgtctggaaa agaagcagag aagctgctga 480
cagagaaggg gaagcatggc agtttcctcg tccgggagag ccagagccac cctggggact 540
tcgtcctctc cgtccgcact ggtgatgaca aaggggagag caatgacagc aagtccaaag 600
tgacccatgt catgatccgc tgtcaggagc tgaaatatga tgttggtgga ggagagcgct 660
ttgactcttt gacagacctg gtggagcatt acaagaagaa ccccatggtg gagacactgg 720
gcacagtcct gcagctcaaa cagcccctca acacaactcg tattaatgcc gctgaaatcg 780
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aaggacagag acaagaaaat aaaaacaaaa atagatacaa aaacatcctg ccctttgatc 960
ataccagggt tgtcctgcac gatggggatc ccaacgagcc agtttctgat tacatcaatg 1020
ccaacatcat catgcctgaa tttgaaacca agtgcaacaa ttcaaaaccc aaaaagagtt 1080
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aggagaactc tcgagtcatt gtcatgacca caaaggaagt ggagagaggg aagagcaagt 1200
gtgtcaagta ctggcctgat gagtgtgcac tcaaagagta tggcgtcatg cgtgtgagga 1260
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gtgtgcctag tgaccctgga ggtgtgctgg acttcctgga ggaggtccac cacaagcagg 1440
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gaacgttcat tgtgattgat atccttattg acatcatccg agagaaaggt gtggactgtg 1560
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caccctgtgc ggaaatgcgg gaggacagcg ctcgagtcta tgagaacgtg ggcctcatgc 1860
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cggggttgac tgactgcctt ttgagaagcg aagtttggaa ccatttgaaa gagcacgtgc 2040
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ttgtcatgga attggttttg aattgtgaag cagctaaatt gtgctctgta ttttctacat 2160
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agacctgtta agaccg 2236

<210> 16
<211> 593
<212> PRT
<213> Rattus norvegicus

<400> 16

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Met Thr Ser Arg Arg Trp Phe His Pro Asn Ile Thr Gly Val Glu Ala
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Glu Asn Leu Leu Leu Thr Arg Gly Val Asp Gly Ser Phe Leu Ala Arg
            20                  25                  30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
        35                  40                  45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
    50                  55                  60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Pro Glu Leu Val Gln Tyr
65                  70                  75                  80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
                85                  90                  95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
            100                 105                 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
        115                 120                 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145                 150                 155                 160
Asn Asp Ser Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
                165                 170                 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
            180                 185                 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
        195                 200                 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
    210                 215                 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
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Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
        275                 280                 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
                325                 330                 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Cys Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Arg Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
                405                 410                 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
        435                 440                 445
Ile Val Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
    450                 455                 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Ser Leu Val Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
                565                 570                 575
Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Arg Ser Phe
            580                 585                 590
Arg
```

<210> 17
<211> 2287
<212> DNA
<213> Homo sapiens

<400> 17
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gggggcctg agcctctccg ccggcgcagg ctctgctcgc gccagctcgc tcccgcagcc 60
atgcccacca ccatcgagcg ggagttcgaa gagttggata ctcagcgtcg ctggcagccg 120
ctgtacttgg aaattcgaaa tgagtcccat gactatcctc atagagtggc caagtttcca 180
gaaaacagaa atcgaaacag atacagagat gtaagcccat atgatcacag tcgtgttaaa 240
ctgcaaaatg ctgagaatga ttatattaat gccagtttag ttgacataga agaggcacaa 300
aggagttaca tcttaacaca gggtccactt cctaacacat gctgccattt ctggcttatg 360
gtttggcagc agaagaccaa agcagttgtc atgctgaacc gcattgtgga gaaagaatcg 420
gttaaatgtg cacagtactg gccaacagat gaccaagaga tgctgtttaa agaaacagga 480
```

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ttcagtgtga agctcttgtc agaagatgtg aagtcgtatt atacagtaca tctactacaa 540
ttagaaaata tcaatagtgg tgaaaccaga acaatatctc actttcatta tactacctgg 600
ccagattttg gagtccctga atcaccagct tcatttctca atttcttgtt taaagtgaga 660
gaatctggct ccttgaaccc tgaccatggg cctgcggtga tccactgtag tgcaggcatt 720
gggcgctctg gcaccttctc tctggtagac acttgtcttg ttttgatgga aaaaggagat 780
gatattaaca taaaacaagt gttactgaac atgagaaaat accgaatggg tcttattcag 840
accccagatc aactgagatt ctcatacatg gctataatag aaggagcaaa atgtataaag 900
ggagattcta gtatacagaa acgatggaaa gaactttcta aggaagactt atctcctgcc 960
tttgatcatt caccaaacaa aataatgact gaaaaataca atgggaacag aataggtcta 1020
gaagaagaaa aactgacagg tgaccgatgt acaggacttt cctctaaaat gcaagataca 1080
atggaggaga acagtgagag tgctctacgg aaacgtattc gagaggacag aaaggccacc 1140
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aggtggttat attggcaacc tattctcact aagatggggt ttatgtcagt cattttggtt 1260
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aactgtaaat ggctgtctaa aataaagaca ttcatgtttg ttaaaaactg gtaaattttg 1560
caactgtatt catacatgtc aaacacagta tttcacctga ccaacattga gatatccttt 1620
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tgaaaaatct gttactaaaa aaaaaaattg tatgtcgatt gaattgtact ggatacattt 1920
tccatttttc taaaaagaag tttgatatga gcagttagaa gttggaataa gcaatttcta 1980
ctatatattg catttctttt atgttttaca gttttcccca ttttaaaaag aaaagcaaac 2040
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tcaggtaaac agttggtcaa gactttgtaa agaaattggt ttctgtaaat cccattattg 2160
atatgtttat ttttcatgaa aatttcaatg tagttggggt agattatgat ttaggaagca 2220
aaagtaagaa gcagcatttt atgattcata atttcagttt actagactga agttttgaag 2280
taaaccc                                                          2287
```

<210> 18
<211> 415
<212> PRT
<213> Homo sapiens

<400> 18

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Met Pro Thr Thr Ile Glu Arg Glu Phe Glu Glu Leu Asp Thr Gln Arg
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Arg Trp Gln Pro Leu Tyr Leu Glu Ile Arg Asn Glu Ser His Asp Tyr
            20                  25                  30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
        35                  40                  45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Asn Ala
    50                  55                  60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
65                  70                  75                  80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
                85                  90                  95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Lys Ala Val Val Met Leu
            100                 105                 110
Asn Arg Ile Val Glu Lys Glu Ser Val Lys Cys Ala Gln Tyr Trp Pro
        115                 120                 125
Thr Asp Asp Gln Glu Met Leu Phe Lys Glu Thr Gly Phe Ser Val Lys
    130                 135                 140
Leu Leu Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val His Leu Leu Gln
145                 150                 155                 160
```

```
Leu Glu Asn Ile Asn Ser Gly Glu Thr Arg Thr Ile Ser His Phe His
                165                 170                 175
Tyr Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe
            180                 185                 190
Leu Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Asn Pro Asp
        195                 200                 205
His Gly Pro Ala Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly
    210                 215                 220
Thr Phe Ser Leu Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Asp
225                 230                 235                 240
Asp Ile Asn Ile Lys Gln Val Leu Leu Asn Met Arg Lys Tyr Arg Met
                245                 250                 255
Gly Leu Ile Gln Thr Pro Asp Gln Leu Arg Phe Ser Tyr Met Ala Ile
            260                 265                 270
Ile Glu Gly Ala Lys Cys Ile Lys Gly Asp Ser Ser Ile Gln Lys Arg
        275                 280                 285
Trp Lys Glu Leu Ser Lys Glu Asp Leu Ser Pro Ala Phe Asp His Ser
    290                 295                 300
Pro Asn Lys Ile Met Thr Glu Lys Tyr Asn Gly Asn Arg Ile Gly Leu
305                 310                 315                 320
Glu Glu Glu Lys Leu Thr Gly Asp Arg Cys Thr Gly Leu Ser Ser Lys
                325                 330                 335
Met Gln Asp Thr Met Glu Glu Asn Ser Glu Ser Ala Leu Arg Lys Arg
            340                 345                 350
Ile Arg Glu Asp Arg Lys Ala Thr Thr Ala Gln Lys Val Gln Gln Met
        355                 360                 365
Lys Gln Arg Leu Asn Glu Asn Glu Arg Lys Arg Lys Arg Trp Leu Tyr
    370                 375                 380
Trp Gln Pro Ile Leu Thr Lys Met Gly Phe Met Ser Val Ile Leu Val
385                 390                 395                 400
Gly Ala Phe Val Gly Trp Arg Leu Phe Phe Gln Gln Asn Ala Leu
                405                 410                 415
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<210> 19
<211> 462
<212> DNA
<213> Homo sapiens

<400> 19
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cagaggctaa atgagaatga acgaaaaaga aaaaggccaa gattgacaga cacctaatat 120
tcatgactta agaatattct gcagctataa attttgaacc attgatgtgc aaagcaagac 180
ctgaagccca ctccggaaac taaagtgagg ctcgctaacc ctctagattg cctcacagtt 240
gtttgtttac aaagtaaact ttacatccag gggatgaaga gcacccacca gcagaagact 300
ttgcagaacc tttaattgga tgtgttaagt gtttttaatg agtgtatgaa atgtagaaag 360
atgtacaaga aataaattag gagagattac tttgtattgt actgccattc ctactgtatt 420
tttatacttt ttggcagcat taaatatttt tgttaaatag tc 462

<210> 20
<211> 462
<212> DNA
<213> Homo sapiens

<400> 20
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cagaggctaa atgagaatga acgaaaaaga aaaaggccaa gattgacaga cacctaatat 120
tcatgactta agaatattct gcagctataa attttgaacc attgatgtgc aaagcaagac 180

ctgaagccca ctccggaaac taaagtgagg ctcgctaacc ctctagattg cctcacagtt 240
gtttgtttac aaagtaaact ttacatccag gggatgaaga gcacccacca gcagaagact 300
ttgcagaacc tttaattgga tgtgttaagt gtttttaatg agtgtatgaa atgtagaaag 360
atgtacaaga aataaattag gagagattac tttgtattgt actgccattc ctactgtatt 420
tttatacttt ttggcagcat taaatatttt tgttaaatag tc 462

<210> 21
<211> 1555
<212> DNA
<213> Mus musculus

<400> 21
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gccgccatgt cggcaaccat cgagcgggag ttcgaggaac tggatgctca gtgtcgctgg 120
cagccgttat acttggaaat tcgaaatgaa tcccatgact atcctcatag agtggccaag 180
tttccagaaa acagaaaccg aaacagatac agagatgtaa gcccatatga tcacagtcgt 240
gttaaactgc aaagtactga aaatgattat attaatgcca gcttagttga catagaagag 300
gcacaaagaa gttacatctt aacacagggc ccacttccga acacatgctg ccatttctgg 360
ctcatggtgt ggcagcaaaa gaccaaagca gttgtcatgc taaaccgaac tgtagaaaaa 420
gaatcggtta aatgtgcaca gtactggcca acggatgaca gagaaatggt gtttaaggaa 480
acgggattca gtgtgaagct cttatctgaa gatgtaaaat catattatac agtacatcta 540
ctacagttag aaaatatcaa tactggtgaa acgagaacca tatctcactt ccattatacc 600
acctggccag attttggggt tccagagtca ccagcttcat ttctaaactt cttgtttaaa 660
gttagagaat ctggttgttt gacccctgac catggacctg cagtgatcca ttgcagtgcg 720
ggcatcgggc gctctggcac cttctctctt gtagatacct gtcttgttct gatggaaaaa 780
ggagaggatg ttaatgtgaa acaattatta ctgaatatga gaaagtatcg aatgggactt 840
attcagacac cggaccaact cagattctcc tacatggcca taatagaagg agcaaagtac 900
acaaaaggag attcaaatat acagaaacgg tggaaagaac tttctaaaga agatttatct 960
cctatttgtg atcattcaca gaacagagtg atggttgaga agtacaatgg gaagagaata 1020
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agcagtgaga gcattctacg gaaacgtatt cgagaggata gaaaggctac gacggctcag 1140
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ttgacagaca cctaaatgtt catgacttga gactattctg cagctataaa atttgaacct 1260
ttgatgtgca aagcaagacc tgaagcccac tccggaaact aaagtgaggc ttgctaaccc 1320
tgtagattgc ctcacaagtt gtctgtttac aaagtaagct ttccatccag gggatgaaga 1380
acgccaccag cagaagactt gcaaaccctt taatttgatg tattgttttt taacatgtgt 1440
atgaaatgta gaaagatgta aaggaaataa attaggagcg actactttgt attgtactgc 1500
cattcctaat gtatttttat acttttggc agcattaaat atttttatta aatag 1555

<210> 22
<211> 382
<212> PRT
<213> Mus musculus

<400> 22
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Arg Trp Gln Pro Leu Tyr Leu Glu Ile Arg Asn Glu Ser His Asp Tyr
20 25 30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
35 40 45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Ser Thr
50 55 60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
65 70 75 80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
85 90 95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Lys Ala Val Val Met Leu

```
            100                 105                 110
Asn Arg Thr Val Glu Lys Glu Ser Val Lys Cys Ala Gln Tyr Trp Pro
        115                 120                 125
Thr Asp Asp Arg Glu Met Val Phe Lys Glu Thr Gly Phe Ser Val Lys
    130                 135                 140
Leu Leu Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val His Leu Leu Gln
145                 150                 155                 160
Leu Glu Asn Ile Asn Thr Gly Glu Thr Arg Thr Ile Ser His Phe His
                165                 170                 175
Tyr Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe
            180                 185                 190
Leu Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Cys Leu Thr Pro Asp
        195                 200                 205
His Gly Pro Ala Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly
    210                 215                 220
Thr Phe Ser Leu Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Glu
225                 230                 235                 240
Asp Val Asn Val Lys Gln Leu Leu Leu Asn Met Arg Lys Tyr Arg Met
                245                 250                 255
Gly Leu Ile Gln Thr Pro Asp Gln Leu Arg Phe Ser Tyr Met Ala Ile
            260                 265                 270
Ile Glu Gly Ala Lys Tyr Thr Lys Gly Asp Ser Asn Ile Gln Lys Arg
        275                 280                 285
Trp Lys Glu Leu Ser Lys Glu Asp Leu Ser Pro Ile Cys Asp His Ser
    290                 295                 300
Gln Asn Arg Val Met Val Glu Lys Tyr Asn Gly Lys Arg Ile Gly Ser
305                 310                 315                 320
Glu Asp Glu Lys Leu Thr Gly Leu Pro Ser Lys Val Gln Asp Thr Val
                325                 330                 335
Glu Glu Ser Ser Glu Ser Ile Leu Arg Lys Arg Ile Arg Glu Asp Arg
            340                 345                 350
Lys Ala Thr Thr Ala Gln Lys Val Gln Gln Met Lys Gln Arg Leu Asn
        355                 360                 365
Glu Thr Glu Arg Lys Arg Lys Arg Pro Arg Leu Thr Asp Thr
    370                 375                 380
```

<210> 23
<211> 1494
<212> DNA
<213> Rattus novegicus

<400> 23

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cctcatagag tggccaagtt tccagaaaac agaaatcgaa acagatacag agatgtaagc 180
ccatatgatc acagtcgtgt taaactgcag agtgctgaaa atgattatat taatgccagc 240
ttagttgaca tagaagaggc acaaagaagt tacatcttaa cacagggccc acttcctaac 300
acgtgctgcc atttctggct catggtgtgg cagcaaaaga ccagagcagt tgtcatgcta 360
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gagatggtgt ttaaggaaac aggattcagc gtgaagctct tatctgaaga tgtgaaatca 480
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<210> 24
<211> 363
<212> PRT
<213> Rattus norvegicus

<400> 24
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20 25 30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
35 40 45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Ser Ala
50 55 60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
65 70 75 80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
85 90 95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Arg Ala Val Val Met Leu
100 105 110
Asn Arg Thr Val Glu Lys Glu Ser Val Lys Cys Ala Gln Tyr Trp Pro
115 120 125
Thr Asp Asp Arg Glu Met Val Phe Lys Glu Thr Gly Phe Ser Val Lys
130 135 140
Leu Leu Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val His Leu Leu Gln
145 150 155 160
Leu Glu Asn Ile Asn Ser Gly Glu Thr Arg Thr Ile Ser His Phe His
165 170 175
Tyr Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe
180 185 190
Leu Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Asn Pro Asp
195 200 205
His Gly Pro Ala Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly
210 215 220
Thr Phe Ser Leu Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Glu
225 230 235 240
Asp Val Asn Val Lys Gln Ile Leu Leu Ser Met Arg Lys Tyr Arg Met
245 250 255
Gly Leu Ile Gln Thr Pro Asp Gln Leu Arg Phe Ser Tyr Met Ala Ile
260 265 270
Ile Glu Gly Ala Lys Tyr Thr Lys Gly Asp Ser Asn Ile Gln Asn Arg
275 280 285
Thr Met Thr Glu Lys Tyr Asn Gly Lys Arg Ile Gly Ser Glu Asp Glu
290 295 300
Lys Leu Thr Gly Leu Ser Ser Lys Val Pro Asp Thr Val Glu Glu Ser
305 310 315 320
Ser Glu Ser Ile Leu Arg Lys Arg Ile Arg Glu Asp Arg Lys Ala Thr

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                325                 330                 335
Thr Ala Gln Lys Val Gln Gln Met Arg Gln Arg Leu Asn Glu Thr Glu
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<210> 25
<211> 2543
<212> DNA
<213> Homo sapiens

<400> 25

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ggagctgtca cccacatcaa gattcagaac actggtgatt actatgacct gtatggaggg 360
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<210> 26

<211> 593
<212> PRT
<213> Homo sapiens

<400> 26

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Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
        35                  40                  45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
    50                  55                  60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65                  70                  75                  80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
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Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
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Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
        115                 120                 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145                 150                 155                 160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
                165                 170                 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
            180                 185                 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
        195                 200                 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
    210                 215                 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
        275                 280                 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
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Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
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Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
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Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
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            420                 425                 430
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Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
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Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Arg Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Pro Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
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<210> 27
<211> 2276
<212> DNA
<213> Homo sapiens

<400> 27

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atgacctgta tggaggggag aaatttgcca ctttggctga gttggtccag tattacatgg 360
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actgtgcaga tcctacctct gaaaggtggt ttcatggaca tctctctggg aaagaagcag 480
agaaattatt aactgaaaaa ggaaaacatg gtagttttct tgtacgagag agccagagcc 540
accctggaga ttttgttctt tctgtgcgca ctggtgatga caaaggggag agcaatgacg 600
gcaagtctaa agtgacccat gttatgattc gctgtcagga actgaaatac gacgttggtg 660
gaggagaacg gtttgattct ttgacagatc ttgtggaaca ttataagaag aatcctatgg 720
tggaaacatt gggtacagta ctacaactca agcagcccct taacacgact cgtataaatg 780
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gtgttgactg cgatattgac gttcccaaaa ccatccagat ggtgcggtct cagaggtcag 1620
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<210> 28
<211> 593
<212> PRT
<213> Homo sapiens

<400> 28

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| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Glu | Asn | Leu | Leu | Leu | Thr | Arg | Gly | Val | Asp | Gly | Ser | Phe | Leu | Ala | Arg |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Pro | Ser | Lys | Ser | Asn | Pro | Gly | Asp | Phe | Thr | Leu | Ser | Val | Arg | Arg | Asn |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Gly | Ala | Val | Thr | His | Ile | Lys | Ile | Gln | Asn | Thr | Gly | Asp | Tyr | Tyr | Asp |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Leu | Tyr | Gly | Gly | Glu | Lys | Phe | Ala | Thr | Leu | Ala | Glu | Leu | Val | Gln | Tyr |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Tyr | Met | Glu | His | His | Gly | Gln | Leu | Lys | Glu | Lys | Asn | Gly | Asp | Val | Ile |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Glu | Leu | Lys | Tyr | Pro | Leu | Asn | Cys | Ala | Asp | Pro | Thr | Ser | Glu | Arg | Trp |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Phe | His | Gly | His | Leu | Ser | Gly | Lys | Glu | Ala | Glu | Lys | Leu | Leu | Thr | Glu |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Lys | Gly | Lys | His | Gly | Ser | Phe | Leu | Val | Arg | Glu | Ser | Gln | Ser | His | Pro |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Gly | Asp | Phe | Val | Leu | Ser | Val | Arg | Thr | Gly | Asp | Asp | Lys | Gly | Glu | Ser |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Asn | Asp | Gly | Lys | Ser | Lys | Val | Thr | His | Val | Met | Ile | Arg | Cys | Gln | Glu |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Leu | Lys | Tyr | Asp | Val | Gly | Gly | Gly | Glu | Arg | Phe | Asp | Ser | Leu | Thr | Asp |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Leu | Val | Glu | His | Tyr | Lys | Lys | Asn | Pro | Met | Val | Glu | Thr | Leu | Gly | Thr |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Val | Leu | Gln | Leu | Lys | Gln | Pro | Leu | Asn | Thr | Thr | Arg | Ile | Asn | Ala | Ala |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Glu | Ile | Glu | Ser | Arg | Val | Arg | Glu | Leu | Ser | Lys | Leu | Ala | Glu | Thr | Thr |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Asp | Lys | Val | Lys | Gln | Gly | Phe | Trp | Glu | Glu | Phe | Glu | Thr | Leu | Gln | Gln |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Gln | Glu | Cys | Lys | Leu | Leu | Tyr | Ser | Arg | Lys | Glu | Gly | Gln | Arg | Gln | Glu |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Asn | Lys | Asn | Lys | Asn | Arg | Tyr | Lys | Asn | Ile | Leu | Pro | Phe | Asp | His | Thr |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Arg | Val | Val | Leu | His | Asp | Gly | Asp | Pro | Asn | Glu | Pro | Val | Ser | Asp | Tyr |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Ile | Asn | Ala | Asn | Ile | Ile | Met | Pro | Glu | Phe | Glu | Thr | Lys | Cys | Asn | Asn |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 |

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Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
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Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
                405                 410                 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
        435                 440                 445
Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
    450                 455                 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Ser Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
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Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Lys Ser Phe
            580                 585                 590
Arg
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<210> 29
<211> 2121
<212> DNA
<213> Homo sapiens

<400> 29

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ctacaactca agcagcccct taacacgact cgtataaatg ctgctgaaat agaaagcaga 840
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<210> 30
<211> 593
<212> PRT
<213> Homo sapiens

<400> 30
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Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
35 40 45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65 70 75 80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
85 90 95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
100 105 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
115 120 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
130 135 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145 150 155 160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
165 170 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
180 185 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
195 200 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
210 215 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr

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225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
        275                 280                 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
                325                 330                 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
                405                 410                 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
        435                 440                 445
Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
    450                 455                 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Ser Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
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Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Lys Ser Phe
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<210> 31
<211> 1980
<212> DNA
<213> Homo sapiens

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<210> 32
<211> 593
<212> PRT
<213> Homo sapiens

<400> 32
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Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
        35                  40                  45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
    50                  55                  60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65                  70                  75                  80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
                85                  90                  95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
            100                 105                 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
        115                 120                 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145                 150                 155                 160

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Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
                165                 170                 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
            180                 185                 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
        195                 200                 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
    210                 215                 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
        275                 280                 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
                325                 330                 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
                405                 410                 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
        435                 440                 445
Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
    450                 455                 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Ser Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
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Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Lys Ser Phe
            580                 585                 590
Arg
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<211> 2338
<212> DNA
<213> Homo sapiens

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ggccagcccg atgtgaccga gcccagcgga gcctgagcaa ggagcgggtc cgtcgcggag 180
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aagattcaga acactggtga ttactatgac ctgtatggag gggagaaatt tgccactttg 420
gctgagttgg tccagtatta catggaacat cacgggcaat taaaagagaa gaatggagat 480
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gatgacaaag gggagagcaa tgacggcaag tctaaagtga cccatgttat gattcgctgt 720
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gaacattata agaagaatcc tatggtggaa acattgggta cagtactaca actcaagcag 840
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<210> 34
<211> 274
<212> DNA
<213> Homo sapiens

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atcatggatg cagggccggt cgtggtgcac tgca 274

<210> 35
<211> 91
<212> PRT
<213> Homo sapiens

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Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
35 40 45
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
50 55 60
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
65 70 75 80
Ile Met Asp Ala Gly Pro Val Val Val His Cys
85 90

<210> 36
<211> 90
<212> DNA
<213> Homo sapiens

<400> 36
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gaccctgggg gcgtgctgga cttcctggag 90

<210> 37
<211> 3984
<212> DNA
<213> Homo sapiens

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<210> 38
<211> 913
<212> PRT
<213> Homo sapiens

<400> 38
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Ile His Phe Leu Asp Gly Val Val Gln Thr Phe Lys Val Thr Lys Gln
35 40 45
Asp Thr Gly Gln Val Leu Leu Asp Met Val His Asn His Leu Gly Val

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    50                  55                  60
Thr Glu Lys Glu Tyr Phe Gly Leu Gln His Asp Asp Asp Ser Val Asp
65                  70                  75                  80
Ser Pro Arg Trp Leu Glu Ala Ser Lys Pro Ile Arg Lys Gln Leu Lys
                85                  90                  95
Gly Gly Phe Pro Cys Thr Leu His Phe Arg Val Arg Phe Phe Ile Pro
            100                 105                 110
Asp Pro Asn Thr Leu Gln Gln Glu Gln Thr Arg His Leu Tyr Phe Leu
        115                 120                 125
Gln Leu Lys Met Asp Ile Cys Glu Gly Arg Leu Thr Cys Pro Leu Asn
    130                 135                 140
Ser Ala Val Val Leu Ala Ser Tyr Ala Val Gln Ser His Phe Gly Asp
145                 150                 155                 160
Tyr Asn Ser Ser Ile His His Pro Gly Tyr Leu Ser Asp Ser His Phe
                165                 170                 175
Ile Pro Asp Gln Asn Glu Asp Phe Leu Thr Lys Val Glu Ser Leu His
            180                 185                 190
Glu Gln His Ser Gly Leu Lys Gln Ser Glu Ala Glu Ser Cys Tyr Ile
        195                 200                 205
Asn Ile Ala Arg Thr Leu Asp Phe Tyr Gly Val Glu Leu His Ser Gly
    210                 215                 220
Arg Asp Leu His Asn Leu Asp Leu Met Ile Gly Ile Ala Ser Ala Gly
225                 230                 235                 240
Val Ala Val Tyr Arg Lys Tyr Ile Cys Thr Ser Phe Tyr Pro Trp Val
                245                 250                 255
Asn Ile Leu Lys Ile Ser Phe Lys Arg Lys Lys Phe Phe Ile His Gln
            260                 265                 270
Arg Gln Lys Gln Ala Glu Ser Arg Glu His Ile Val Ala Phe Asn Met
        275                 280                 285
Leu Asn Tyr Arg Ser Cys Lys Asn Leu Trp Lys Ser Cys Val Glu His
    290                 295                 300
His Thr Phe Phe Gln Ala Lys Lys Leu Leu Pro Gln Glu Lys Asn Val
305                 310                 315                 320
Leu Ser Gln Tyr Trp Thr Met Gly Ser Arg Asn Thr Lys Lys Ser Val
                325                 330                 335
Asn Asn Gln Tyr Cys Lys Lys Val Ile Gly Gly Met Val Trp Asn Pro
            340                 345                 350
Ala Met Arg Arg Ser Leu Ser Val Glu His Leu Glu Thr Lys Ser Leu
        355                 360                 365
Pro Ser Arg Ser Pro Pro Ile Thr Pro Asn Trp Arg Ser Pro Arg Leu
    370                 375                 380
Arg His Glu Ile Arg Lys Pro Arg His Ser Ser Ala Asp Asn Leu Ala
385                 390                 395                 400
Asn Glu Met Thr Tyr Ile Thr Glu Thr Glu Asp Val Phe Tyr Thr Tyr
                405                 410                 415
Lys Gly Ser Leu Ala Pro Gln Asp Ser Asp Ser Glu Val Ser Gln Asn
            420                 425                 430
Arg Ser Pro His Gln Glu Ser Leu Ser Glu Asn Asn Pro Ala Gln Ser
        435                 440                 445
Tyr Leu Thr Gln Lys Ser Ser Ser Ser Val Ser Pro Ser Ser Asn Ala
    450                 455                 460
Pro Gly Ser Cys Ser Pro Asp Gly Val Asp Gln Gln Leu Leu Asp Asp
465                 470                 475                 480
Phe His Arg Val Thr Lys Gly Gly Ser Thr Glu Asp Ala Ser Gln Tyr
                485                 490                 495
Tyr Cys Asp Lys Asn Asp Asn Gly Asp Ser Tyr Leu Val Leu Ile Arg
            500                 505                 510
Ile Thr Pro Asp Glu Asp Gly Lys Phe Gly Phe Asn Leu Lys Gly Gly
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        515                 520                 525
Val Asp Gln Lys Met Pro Leu Val Val Ser Arg Ile Asn Pro Glu Ser
    530                 535                 540
Pro Ala Asp Thr Cys Ile Pro Lys Leu Asn Glu Gly Asp Gln Ile Val
545                 550                 555                 560
Leu Ile Asn Gly Arg Asp Ile Ser Glu His Thr His Asp Gln Val Val
                565                 570                 575
Met Phe Ile Lys Ala Ser Arg Glu Ser His Ser Arg Glu Leu Ala Leu
            580                 585                 590
Val Ile Arg Arg Arg Ala Val Arg Ser Phe Ala Asp Phe Lys Ser Glu
        595                 600                 605
Asp Glu Leu Asn Gln Leu Phe Pro Glu Ala Ile Phe Pro Met Cys Pro
    610                 615                 620
Glu Gly Gly Asp Thr Leu Glu Gly Ser Met Ala Gln Leu Lys Lys Gly
625                 630                 635                 640
Leu Glu Ser Gly Thr Val Leu Ile Gln Phe Glu Gln Leu Tyr Arg Lys
                645                 650                 655
Lys Pro Gly Leu Ala Ile Thr Phe Ala Lys Leu Pro Gln Asn Leu Asp
            660                 665                 670
Lys Asn Arg Tyr Lys Asp Val Leu Pro Tyr Asp Thr Thr Arg Val Leu
        675                 680                 685
Leu Gln Gly Asn Glu Asp Tyr Ile Asn Ala Ser Tyr Val Asn Met Glu
    690                 695                 700
Ile Pro Ala Ala Asn Leu Val Asn Lys Tyr Ile Ala Thr Gln Gly Pro
705                 710                 715                 720
Leu Pro His Thr Cys Ala Gln Phe Trp Gln Val Val Trp Asp Gln Lys
                725                 730                 735
Leu Ser Leu Ile Val Met Leu Thr Thr Leu Thr Glu Arg Gly Arg Thr
            740                 745                 750
Lys Cys His Gln Tyr Trp Pro Asp Pro Pro Asp Val Met Asn His Gly
        755                 760                 765
Gly Phe His Ile Gln Cys Gln Ser Glu Asp Cys Thr Ile Ala Tyr Val
    770                 775                 780
Ser Arg Glu Met Leu Val Thr Asn Thr Gln Thr Gly Glu Glu His Thr
785                 790                 795                 800
Val Thr His Leu Gln Tyr Val Ala Trp Pro Asp His Gly Ile Pro Asp
                805                 810                 815
Asp Ser Ser Asp Phe Leu Glu Phe Val Asn Tyr Val Arg Ser Leu Arg
            820                 825                 830
Val Asp Ser Glu Pro Val Leu Val His Cys Ser Ala Gly Ile Gly Arg
        835                 840                 845
Thr Gly Val Leu Val Thr Met Glu Thr Ala Met Cys Leu Thr Glu Arg
    850                 855                 860
Asn Leu Pro Ile Tyr Pro Leu Asp Ile Val Arg Lys Met Arg Asp Gln
865                 870                 875                 880
Arg Ala Met Met Val Gln Thr Ser Ser Gln Tyr Lys Phe Val Cys Glu
                885                 890                 895
Ala Ile Leu Arg Val Tyr Glu Glu Gly Leu Val Gln Met Leu Asp Pro
            900                 905                 910
Ser
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<210> 39
<211> 2111
<212> DNA
<213> Homo sapiens

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tgattggaat tgcttccgcg ggtgttgctg tgtaccgaaa atacatttgc acaagtttct 180
atccttgggt gaacattctc aaaatttctt tcaaaaggaa aaagttcttc atacatcagc 240
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tactacctca ggaaaagaat gttctgtctc agtactggac tatgggctct cggaacacca 420
aaaagtcggt aaataaccaa tattgcaaaa aggtgattgg cgggatggtg tggaacccag 480
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ttgtgtgtga a 2111

<210> 40
<211> 703
<212> PRT
<213> Homo sapiens

<400> 40
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20 25 30
Asp Leu His Asn Leu Asp Leu Met Ile Gly Ile Ala Ser Ala Gly Val
35 40 45
Ala Val Tyr Arg Lys Tyr Ile Cys Thr Ser Phe Tyr Pro Trp Val Asn
50 55 60
Ile Leu Lys Ile Ser Phe Lys Arg Lys Lys Phe Phe Ile His Gln Arg
65 70 75 80
Gln Lys Gln Ala Glu Ser Arg Glu His Ile Val Ala Phe Asn Met Leu
85 90 95
Asn Tyr Arg Ser Cys Lys Asn Leu Trp Lys Ser Cys Val Glu His His
100 105 110

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Thr Phe Phe Gln Ala Lys Lys Leu Leu Pro Gln Glu Lys Asn Val Leu
      115                 120                 125
Ser Gln Tyr Trp Thr Met Gly Ser Arg Asn Thr Lys Lys Ser Val Asn
    130                 135                 140
Asn Gln Tyr Cys Lys Lys Val Ile Gly Gly Met Val Trp Asn Pro Ala
145                 150                 155                 160
Met Arg Arg Ser Leu Ser Val Glu His Leu Glu Thr Lys Ser Leu Pro
                165                 170                 175
Ser Arg Ser Pro Pro Ile Thr Pro Asn Trp Arg Ser Pro Arg Leu Arg
            180                 185                 190
His Glu Ile Arg Lys Pro Arg His Ser Ser Ala Asp Asn Leu Ala Asn
        195                 200                 205
Glu Met Thr Tyr Ile Thr Glu Thr Glu Asp Val Phe Tyr Thr Tyr Lys
    210                 215                 220
Gly Ser Leu Ala Pro Gln Asp Ser Asp Ser Glu Val Ser Gln Asn Arg
225                 230                 235                 240
Ser Pro His Gln Glu Ser Leu Ser Glu Asn Asn Pro Ala Gln Ser Tyr
                245                 250                 255
Leu Thr Gln Lys Ser Ser Ser Ser Val Ser Pro Ser Ser Asn Ala Pro
            260                 265                 270
Gly Ser Cys Ser Pro Asp Gly Val Asp Gln Gln Leu Leu Asp Asp Phe
        275                 280                 285
His Arg Val Thr Lys Gly Gly Ser Thr Glu Asp Ala Ser Gln Tyr Tyr
    290                 295                 300
Cys Asp Lys Asn Asp Asn Gly Asp Ser Tyr Leu Val Leu Ile Arg Ile
305                 310                 315                 320
Thr Pro Asp Glu Asp Gly Lys Phe Gly Phe Asn Leu Lys Gly Gly Val
                325                 330                 335
Asp Gln Lys Met Pro Leu Val Val Ser Arg Ile Asn Pro Glu Ser Pro
            340                 345                 350
Ala Asp Thr Cys Ile Pro Lys Leu Asn Glu Gly Asp Gln Ile Val Leu
        355                 360                 365
Ile Asn Gly Arg Asp Ile Ser Glu His Thr His Asp Gln Val Val Met
    370                 375                 380
Phe Ile Lys Ala Ser Arg Glu Ser His Ser Arg Glu Leu Ala Leu Val
385                 390                 395                 400
Ile Arg Arg Arg Ala Val Arg Ser Phe Ala Asp Phe Lys Ser Glu Asp
                405                 410                 415
Glu Leu Asn Gln Leu Phe Pro Glu Ala Ile Phe Pro Met Cys Pro Glu
            420                 425                 430
Gly Gly Asp Thr Leu Glu Gly Ser Met Ala Gln Leu Lys Lys Gly Leu
        435                 440                 445
Glu Ser Gly Thr Val Leu Ile Gln Phe Glu Gln Leu Tyr Arg Lys Lys
    450                 455                 460
Pro Gly Leu Ala Ile Thr Phe Ala Lys Leu Pro Gln Asn Leu Asp Lys
465                 470                 475                 480
Asn Arg Tyr Lys Asp Val Leu Pro Tyr Asp Thr Thr Arg Val Leu Leu
                485                 490                 495
Gln Gly Asn Glu Asp Tyr Ile Asn Ala Ser Tyr Val Asn Met Glu Ile
            500                 505                 510
Pro Ala Ala Asn Leu Val Asn Lys Tyr Ile Ala Thr Gln Gly Pro Leu
        515                 520                 525
Pro His Thr Cys Ala Gln Phe Trp Gln Val Val Trp Asp Gln Lys Leu
    530                 535                 540
Ser Leu Ile Val Met Leu Thr Thr Leu Thr Glu Arg Gly Arg Thr Lys
545                 550                 555                 560
Cys His Gln Tyr Trp Pro Asp Pro Pro Asp Val Met Asn His Gly Gly
                565                 570                 575
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Phe His Ile Gln Cys Gln Ser Glu Asp Cys Thr Ile Ala Tyr Val Ser
            580                 585                 590
Arg Glu Met Leu Val Thr Asn Thr Gln Thr Gly Glu Glu His Thr Val
        595                 600                 605
Thr His Leu Gln Tyr Val Ala Trp Pro Asp His Gly Ile Pro Asp Asp
    610                 615                 620
Ser Ser Asp Phe Leu Glu Phe Val Asn Tyr Val Arg Ser Leu Arg Val
625                 630                 635                 640
Asp Ser Glu Pro Val Leu Val His Cys Ser Ala Gly Ile Gly Arg Thr
                645                 650                 655
Gly Val Leu Val Thr Met Glu Thr Ala Met Cys Leu Thr Glu Arg Asn
            660                 665                 670
Leu Pro Ile Tyr Pro Leu Asp Ile Val Arg Lys Met Arg Asp Gln Arg
        675                 680                 685
Ala Met Met Val Gln Thr Ser Ser Gln Tyr Lys Phe Val Cys Glu
    690                 695                 700
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<210> 41
<211> 5117
<212> DNA
<213> Homo sapiens

<400> 41

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<210> 42
<211> 1337
<212> PRT

<213> Homo sapiens

<400> 42

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            20                  25                  30
Ile Leu Cys Ala Gly Gly Thr Pro Ser Pro Ile Pro Asp Pro Ser Val
        35                  40                  45
Ala Thr Val Ala Thr Gly Glu Asn Gly Ile Thr Gln Ile Ser Ser Thr
    50                  55                  60
Ala Glu Ser Phe His Lys Gln Asn Gly Thr Gly Thr Pro Gln Val Glu
65                  70                  75                  80
Thr Asn Thr Ser Glu Asp Gly Glu Ser Ser Gly Ala Asn Asp Ser Leu
                85                  90                  95
Arg Thr Pro Glu Gln Gly Ser Asn Gly Thr Asp Gly Ala Ser Gln Lys
            100                 105                 110
Thr Pro Ser Ser Thr Gly Pro Ser Pro Val Phe Asp Ile Lys Ala Val
        115                 120                 125
Ser Ile Ser Pro Thr Asn Val Ile Leu Thr Trp Lys Ser Asn Asp Thr
    130                 135                 140
Ala Ala Ser Glu Tyr Lys Tyr Val Val Lys His Lys Met Glu Asn Glu
145                 150                 155                 160
Lys Thr Ile Thr Val Val His Gln Pro Trp Cys Asn Ile Thr Gly Leu
                165                 170                 175
Arg Pro Ala Thr Ser Tyr Val Phe Ser Ile Thr Pro Gly Ile Gly Asn
            180                 185                 190
Glu Thr Trp Gly Asp Pro Arg Val Ile Lys Val Ile Thr Glu Pro Ile
        195                 200                 205
Pro Val Ser Asp Leu Arg Val Ala Leu Thr Gly Val Arg Lys Ala Ala
    210                 215                 220
Leu Ser Trp Ser Asn Gly Asn Gly Thr Ala Ser Cys Arg Val Leu Leu
225                 230                 235                 240
Glu Ser Ile Gly Ser His Glu Glu Leu Thr Gln Asp Ser Arg Leu Gln
                245                 250                 255
Val Asn Ile Ser Asp Leu Lys Pro Gly Val Gln Tyr Asn Ile Asn Pro
            260                 265                 270
Tyr Leu Leu Gln Ser Asn Lys Thr Lys Gly Asp Pro Leu Gly Thr Glu
        275                 280                 285
Gly Gly Leu Asp Ala Ser Asn Thr Glu Arg Ser Arg Ala Gly Ser Pro
    290                 295                 300
Thr Ala Pro Val His Asp Glu Ser Leu Val Gly Pro Val Asp Pro Ser
305                 310                 315                 320
Ser Gly Gln Gln Ser Arg Asp Thr Glu Val Leu Leu Val Gly Leu Glu
                325                 330                 335
Pro Gly Thr Arg Tyr Asn Ala Thr Val Tyr Ser Gln Ala Ala Asn Gly
            340                 345                 350
Thr Glu Gly Gln Pro Gln Ala Ile Glu Phe Arg Thr Asn Ala Ile Gln
        355                 360                 365
Val Phe Asp Val Thr Ala Val Asn Ile Ser Ala Thr Ser Leu Thr Leu
    370                 375                 380
Ile Trp Lys Val Ser Asp Asn Glu Ser Ser Ser Asn Tyr Thr Tyr Lys
385                 390                 395                 400
Ile His Val Ala Gly Glu Thr Asp Ser Ser Asn Leu Asn Val Ser Glu
                405                 410                 415
Pro Arg Ala Val Ile Pro Gly Leu Arg Ser Ser Thr Phe Tyr Asn Ile
            420                 425                 430
Thr Val Cys Pro Val Leu Gly Asp Ile Glu Gly Thr Pro Gly Phe Leu
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        435                 440                 445
Gln Val His Thr Pro Pro Val Pro Val Ser Asp Phe Arg Val Thr Val
    450                 455                 460
Val Ser Thr Thr Glu Ile Gly Leu Ala Trp Ser Ser His Asp Ala Glu
465                 470                 475                 480
Ser Phe Gln Met His Ile Thr Gln Glu Gly Ala Gly Asn Ser Arg Val
                485                 490                 495
Glu Ile Thr Thr Asn Gln Ser Ile Ile Ile Gly Gly Leu Phe Pro Gly
            500                 505                 510
Thr Lys Tyr Cys Phe Glu Ile Val Pro Lys Gly Pro Asn Gly Thr Glu
        515                 520                 525
Gly Ala Ser Arg Thr Val Cys Asn Arg Thr Val Pro Ser Ala Val Phe
    530                 535                 540
Asp Ile His Val Val Tyr Val Thr Thr Thr Glu Met Trp Leu Asp Trp
545                 550                 555                 560
Lys Ser Pro Asp Gly Ala Ser Glu Tyr Val Tyr His Leu Val Ile Glu
                565                 570                 575
Ser Lys His Gly Ser Asn His Thr Ser Thr Tyr Asp Lys Ala Ile Thr
            580                 585                 590
Leu Gln Gly Leu Ile Pro Gly Thr Leu Tyr Asn Ile Thr Ile Ser Pro
        595                 600                 605
Glu Val Asp His Val Trp Gly Asp Pro Asn Ser Thr Ala Gln Tyr Thr
    610                 615                 620
Arg Pro Ser Asn Val Ser Asn Ile Asp Val Ser Thr Asn Thr Thr Ala
625                 630                 635                 640
Ala Thr Leu Ser Trp Gln Asn Phe Asp Asp Ala Ser Pro Thr Tyr Ser
                645                 650                 655
Tyr Cys Leu Leu Ile Glu Lys Ala Gly Asn Ser Ser Asn Ala Thr Gln
            660                 665                 670
Val Val Thr Asp Ile Gly Ile Thr Asp Ala Thr Val Thr Glu Leu Ile
        675                 680                 685
Pro Gly Ser Ser Tyr Thr Val Glu Ile Phe Ala Gln Val Gly Asp Gly
    690                 695                 700
Ile Lys Ser Leu Glu Pro Gly Arg Lys Ser Phe Cys Thr Asp Pro Ala
705                 710                 715                 720
Ser Met Ala Ser Phe Asp Cys Glu Val Val Pro Lys Glu Pro Ala Leu
                725                 730                 735
Val Leu Lys Trp Thr Cys Pro Pro Gly Ala Asn Ala Gly Phe Glu Leu
            740                 745                 750
Glu Val Ser Ser Gly Ala Trp Asn Asn Ala Thr His Leu Glu Ser Cys
        755                 760                 765
Ser Ser Glu Asn Gly Thr Glu Tyr Arg Thr Glu Val Thr Tyr Leu Asn
    770                 775                 780
Phe Ser Thr Ser Tyr Asn Ile Ser Ile Thr Thr Val Ser Cys Gly Lys
785                 790                 795                 800
Met Ala Ala Pro Thr Arg Asn Thr Cys Thr Thr Gly Ile Thr Asp Pro
                805                 810                 815
Pro Pro Pro Asp Gly Ser Pro Asn Ile Thr Ser Val Ser His Asn Ser
            820                 825                 830
Val Lys Val Lys Phe Ser Gly Phe Glu Ala Ser His Gly Pro Ile Lys
        835                 840                 845
Ala Tyr Ala Val Ile Leu Thr Thr Gly Glu Ala Gly His Pro Ser Ala
    850                 855                 860
Asp Val Leu Lys Tyr Thr Tyr Asp Asp Phe Lys Lys Gly Ala Ser Asp
865                 870                 875                 880
Thr Tyr Val Thr Tyr Leu Ile Arg Thr Glu Glu Lys Gly Arg Ser Gln
                885                 890                 895
Ser Leu Ser Glu Val Leu Lys Tyr Glu Ile Asp Val Gly Asn Glu Ser
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            900                 905                 910
Thr Thr Leu Gly Tyr Tyr Asn Gly Lys Leu Glu Pro Leu Gly Ser Tyr
        915                 920                 925
Arg Ala Cys Val Ala Gly Phe Thr Asn Ile Thr Phe His Pro Gln Asn
    930                 935                 940
Lys Gly Leu Ile Asp Gly Ala Glu Ser Tyr Val Ser Phe Ser Arg Tyr
945                 950                 955                 960
Ser Asp Ala Val Ser Leu Pro Gln Asp Pro Gly Val Ile Cys Gly Ala
                965                 970                 975
Val Phe Gly Cys Ile Phe Gly Ala Leu Val Ile Val Thr Val Gly Gly
            980                 985                 990
Phe Ile Phe Trp Arg Lys Lys Arg Lys Asp Ala Lys Asn Asn Glu Val
        995                 1000                1005
Ser Phe Ser Gln Ile Lys Pro Lys Lys Ser Lys Leu Ile Arg Val Glu
    1010                1015                1020
Asn Phe Glu Ala Tyr Phe Lys Lys Gln Gln Ala Asp Ser Asn Cys Gly
1025                1030                1035                1040
Phe Ala Glu Glu Tyr Glu Asp Leu Lys Leu Val Gly Ile Ser Gln Pro
                1045                1050                1055
Lys Tyr Ala Ala Glu Leu Ala Glu Asn Arg Gly Lys Asn Arg Tyr Asn
            1060                1065                1070
Asn Val Leu Pro Tyr Asp Ile Ser Arg Val Lys Leu Ser Val Gln Thr
        1075                1080                1085
His Ser Thr Asp Asp Tyr Ile Asn Ala Asn Tyr Met Pro Gly Tyr His
    1090                1095                1100
Ser Lys Lys Asp Phe Ile Ala Thr Gln Gly Pro Leu Pro Asn Thr Leu
1105                1110                1115                1120
Lys Asp Phe Trp Arg Met Val Trp Glu Lys Asn Val Tyr Ala Ile Ile
                1125                1130                1135
Met Leu Thr Lys Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu Tyr
            1140                1145                1150
Trp Pro Ser Lys Gln Ala Gln Asp Tyr Gly Asp Ile Thr Val Ala Met
        1155                1160                1165
Thr Ser Glu Ile Val Leu Pro Glu Trp Thr Ile Arg Asp Phe Thr Val
    1170                1175                1180
Lys Asn Ile Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe
1185                1190                1195                1200
Thr Ser Trp Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile
                1205                1210                1215
Asn Phe Arg Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu
            1220                1225                1230
Ser Pro Ile Leu Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr
        1235                1240                1245
Phe Ile Ala Ile Asp Arg Leu Ile Tyr Gln Ile Glu Asn Glu Asn Thr
    1250                1255                1260
Val Asp Val Tyr Gly Ile Val Tyr Asp Leu Arg Met His Arg Pro Leu
1265                1270                1275                1280
Met Val Gln Thr Glu Asp Gln Tyr Val Phe Leu Asn Gln Cys Val Leu
                1285                1290                1295
Asp Ile Val Arg Ser Gln Lys Asp Ser Lys Val Asp Leu Ile Tyr Gln
            1300                1305                1310
Asn Thr Thr Ala Met Thr Ile Tyr Glu Asn Leu Ala Pro Val Thr Thr
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Phe Gly Lys Thr Asn Gly Tyr Ile Ala
    1330                1335
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<210> 43

<211> 4756
<212> DNA
<213> Homo sapiens

<400> 43
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ccccccgcgg cagccgcgct aggctccggc gtgtggccgc ggccgccgcc gccgctgcca 180
tgtctccggg gaagcccggg gcgggcggag cggggacgag gcggaccggc tggcggagga 240
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ggcccgattc gcgcgtccgg ggcacgttcc agggcgcgcg gggcatgaag ccggcggcgc 360
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cttcagtagc aactgttgcc acaggggaaa atggcataac gcagatcagc agtacagcag 540
aatcctttca taaacagaat ggaactggaa cacctcaggt ggaaacaaac accagtgagg 600
atggtgaaag ctctggagcc aacgatagtt taagaacacc tgaacaagga tctaatggga 660
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aagctgtttc catcagtcca accaatgtga tcttaacttg gaaaagtaat gacacagctg 780
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aaccgatccc agtttctgat ctccgtgttg ccctcacggg tgtgaggaag gctgctctct 1020
cctggagcaa tggcaatggc actgcctcct gccgggttct tcttgaaagc attggaagcc 1080
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ttcaatacaa catcaacccg tatcttctac aatcaaataa gacaaaggga gacccccttgg 1200
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tccacgtggt ctacgtcacc accacggaga tgtggctgga ctggaagagc cctgacggtg 2040
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cgtatgacaa agcgattact ctccagggcc tgattccggg caccttatat aacatcacca 2160
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cgggcacttt cattgccatt gatcgtctca tctaccagat agagaatgag aacaccgtgg 4140
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accagtatgt tttcctcaat cagtgtgttt tggatattgt cagatcccag aaagactcaa 4260
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<210> 44
<211> 1337
<212> PRT
<213> Homo sapiens

<400> 44
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Leu Arg Trp Ala Leu Pro Leu Leu Leu Leu Leu Leu Arg Leu Gly Gln
20 25 30
Ile Leu Cys Ala Gly Gly Thr Pro Ser Pro Ile Pro Asp Pro Ser Val
35 40 45
Ala Thr Val Ala Thr Gly Glu Asn Gly Ile Thr Gln Ile Ser Ser Thr
50 55 60
Ala Glu Ser Phe His Lys Gln Asn Gly Thr Gly Thr Pro Gln Val Glu
65 70 75 80
Thr Asn Thr Ser Glu Asp Gly Glu Ser Ser Gly Ala Asn Asp Ser Leu
85 90 95
Arg Thr Pro Glu Gln Gly Ser Asn Gly Thr Asp Gly Ala Ser Gln Lys
100 105 110
Thr Pro Ser Ser Thr Gly Pro Ser Pro Val Phe Asp Ile Lys Ala Val
115 120 125
Ser Ile Ser Pro Thr Asn Val Ile Leu Thr Trp Lys Ser Asn Asp Thr
130 135 140
Ala Ala Ser Glu Tyr Lys Tyr Val Val Lys His Lys Met Glu Asn Glu
145 150 155 160
Lys Thr Ile Thr Val Val His Gln Pro Trp Cys Asn Ile Thr Gly Leu
165 170 175
Arg Pro Ala Thr Ser Tyr Val Phe Ser Ile Thr Pro Gly Ile Gly Asn
180 185 190

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Glu Thr Trp Gly Asp Pro Arg Val Ile Lys Val Ile Thr Glu Pro Ile
        195                 200                 205
Pro Val Ser Asp Leu Arg Val Ala Leu Thr Gly Val Arg Lys Ala Ala
    210                 215                 220
Leu Ser Trp Ser Asn Gly Asn Gly Thr Ala Ser Cys Arg Val Leu Leu
225                 230                 235                 240
Glu Ser Ile Gly Ser His Glu Glu Leu Thr Gln Asp Ser Arg Leu Gln
                245                 250                 255
Val Asn Ile Ser Gly Leu Lys Pro Gly Val Gln Tyr Asn Ile Asn Pro
            260                 265                 270
Tyr Leu Leu Gln Ser Asn Lys Thr Lys Gly Asp Pro Leu Gly Thr Glu
        275                 280                 285
Gly Gly Leu Asp Ala Ser Asn Thr Glu Arg Ser Arg Ala Gly Ser Pro
    290                 295                 300
Thr Ala Pro Val His Asp Glu Ser Leu Val Gly Pro Val Asp Pro Ser
305                 310                 315                 320
Ser Gly Gln Gln Ser Arg Asp Thr Glu Val Leu Leu Val Gly Leu Glu
                325                 330                 335
Pro Gly Thr Arg Tyr Asn Ala Thr Val Tyr Ser Gln Ala Ala Asn Gly
            340                 345                 350
Thr Glu Gly Gln Pro Gln Ala Ile Glu Phe Arg Thr Asn Ala Ile Gln
        355                 360                 365
Val Phe Asp Val Thr Ala Val Asn Ile Ser Ala Thr Ser Leu Thr Leu
    370                 375                 380
Ile Trp Lys Val Ser Asp Asn Glu Ser Ser Ser Asn Tyr Thr Tyr Lys
385                 390                 395                 400
Ile His Val Ala Gly Glu Thr Asp Ser Ser Asn Leu Asn Val Ser Glu
                405                 410                 415
Pro Arg Ala Val Ile Pro Gly Leu Arg Ser Ser Thr Phe Tyr Asn Ile
            420                 425                 430
Thr Val Cys Pro Val Leu Gly Asp Ile Glu Gly Thr Pro Gly Phe Leu
        435                 440                 445
Gln Val His Thr Pro Pro Val Pro Val Ser Asp Phe Arg Val Thr Val
    450                 455                 460
Val Ser Thr Thr Glu Ile Gly Leu Ala Trp Ser Ser His Asp Ala Glu
465                 470                 475                 480
Ser Phe Gln Met His Ile Thr Gln Glu Gly Ala Gly Asn Ser Arg Val
                485                 490                 495
Glu Ile Thr Thr Asn Gln Ser Ile Ile Ile Gly Gly Leu Phe Pro Gly
            500                 505                 510
Thr Lys Tyr Cys Phe Glu Ile Val Pro Lys Gly Pro Asn Gly Thr Glu
        515                 520                 525
Gly Ala Ser Arg Thr Val Cys Asn Arg Thr Val Pro Ser Ala Val Phe
    530                 535                 540
Asp Ile His Val Val Tyr Val Thr Thr Thr Glu Met Trp Leu Asp Trp
545                 550                 555                 560
Lys Ser Pro Asp Gly Ala Ser Glu Tyr Val Tyr His Leu Val Ile Glu
                565                 570                 575
Ser Lys His Gly Ser Asn His Thr Ser Thr Tyr Asp Lys Ala Ile Thr
            580                 585                 590
Leu Gln Gly Leu Ile Pro Gly Thr Leu Tyr Asn Ile Thr Ile Ser Pro
        595                 600                 605
Glu Val Asp His Val Trp Gly Asp Pro Asn Ser Thr Ala Gln Tyr Thr
    610                 615                 620
Arg Pro Ser Asn Val Ser Asn Ile Asp Val Ser Thr Asn Thr Thr Ala
625                 630                 635                 640
Ala Thr Leu Ser Trp Gln Asn Phe Asp Asp Ala Ser Pro Thr Tyr Ser
                645                 650                 655
```

```
Tyr Cys Leu Leu Ile Glu Lys Ala Gly Asn Ser Ser Asn Ala Thr Gln
            660                 665                 670
Val Val Thr Asp Ile Gly Ile Thr Asp Ala Thr Val Thr Glu Leu Ile
        675                 680                 685
Pro Gly Ser Ser Tyr Thr Val Glu Ile Phe Ala Gln Val Gly Asp Gly
    690                 695                 700
Ile Lys Ser Leu Glu Pro Gly Arg Lys Ser Phe Cys Thr Asp Pro Ala
705                 710                 715                 720
Ser Met Ala Ser Phe Asp Cys Glu Val Val Pro Lys Glu Pro Ala Leu
                725                 730                 735
Val Leu Lys Trp Thr Cys Pro Pro Gly Ala Asn Ala Gly Phe Glu Leu
            740                 745                 750
Glu Val Ser Ser Gly Ala Trp Asn Asn Ala Thr His Leu Glu Ser Cys
        755                 760                 765
Ser Ser Glu Asn Gly Thr Glu Tyr Arg Thr Glu Val Thr Tyr Leu Asn
    770                 775                 780
Phe Ser Thr Ser Tyr Asn Ile Ser Ile Thr Thr Val Ser Cys Gly Lys
785                 790                 795                 800
Met Ala Ala Pro Thr Arg Asn Thr Cys Thr Thr Gly Ile Thr Asp Pro
                805                 810                 815
Pro Pro Pro Asp Gly Ser Pro Asn Ile Thr Ser Val Ser His Asn Ser
            820                 825                 830
Val Lys Val Lys Phe Ser Gly Phe Glu Ala Ser His Gly Pro Ile Lys
        835                 840                 845
Ala Tyr Ala Val Ile Leu Thr Thr Gly Glu Ala Gly His Pro Ser Ala
    850                 855                 860
Asp Val Leu Lys Tyr Thr Tyr Asp Asp Phe Lys Lys Gly Ala Ser Asp
865                 870                 875                 880
Thr Tyr Val Thr Tyr Leu Ile Arg Thr Glu Glu Lys Gly Arg Ser Gln
                885                 890                 895
Ser Leu Ser Glu Val Leu Lys Tyr Glu Ile Asp Val Gly Asn Glu Ser
            900                 905                 910
Thr Thr Leu Gly Tyr Leu Gln Trp Glu Ala Gly Thr Ser Gly Leu Leu
        915                 920                 925
Pro Ala Cys Val Ala Gly Phe Thr Asn Ile Thr Phe His Pro Gln Asn
    930                 935                 940
Lys Gly Leu Ile Asp Gly Ala Glu Ser Tyr Val Ser Phe Ser Arg Tyr
945                 950                 955                 960
Ser Asp Ala Val Ser Leu Pro Gln Asp Pro Gly Val Ile Cys Gly Ala
                965                 970                 975
Val Phe Gly Cys Ile Phe Gly Ala Leu Val Ile Val Thr Val Gly Gly
            980                 985                 990
Phe Ile Phe Trp Arg Lys Lys Arg Lys Asp Ala Lys Asn Asn Glu Val
        995                 1000                1005
Ser Phe Ser Gln Ile Lys Pro Lys Lys Ser Lys Leu Ile Arg Val Glu
    1010                1015                1020
Asn Phe Glu Ala Tyr Phe Lys Lys Gln Gln Ala Asp Ser Asn Cys Gly
1025                1030                1035                1040
Phe Ala Glu Glu Tyr Glu Asp Leu Lys Leu Val Gly Ile Ser Gln Pro
                1045                1050                1055
Lys Tyr Ala Ala Glu Leu Ala Glu Asn Arg Gly Lys Asn Arg Tyr Asn
            1060                1065                1070
Asn Val Leu Pro Tyr Asp Ile Ser Arg Val Lys Leu Ser Val Gln Thr
        1075                1080                1085
His Ser Thr Asp Asp Tyr Ile Asn Ala Asn Tyr Met Pro Gly Tyr His
    1090                1095                1100
Ser Lys Lys Asp Phe Ile Ala Thr Gln Gly Pro Leu Pro Asn Thr Leu
1105                1110                1115                1120
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Lys Asp Phe Trp Arg Met Val Trp Glu Lys Asn Val Tyr Ala Ile Ile
                1125                1130                1135
Met Leu Thr Lys Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu Tyr
            1140                1145                1150
Trp Pro Ser Lys Gln Ala Gln Asp Tyr Gly Asp Ile Thr Val Ala Met
        1155                1160                1165
Thr Ser Glu Ile Val Leu Pro Glu Trp Thr Ile Arg Asp Phe Thr Val
    1170                1175                1180
Lys Asn Ile Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe
1185                1190                1195                1200
Thr Ser Trp Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile
                1205                1210                1215
Asn Phe Arg Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu
            1220                1225                1230
Ser Pro Ile Leu Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr
        1235                1240                1245
Phe Ile Ala Ile Asp Arg Leu Ile Tyr Gln Ile Glu Asn Glu Asn Thr
    1250                1255                1260
Val Asp Val Tyr Gly Ile Val Tyr Asp Leu Arg Met His Arg Pro Leu
1265                1270                1275                1280
Met Val Gln Thr Glu Asp Gln Tyr Val Phe Leu Asn Gln Cys Val Leu
                1285                1290                1295
Asp Ile Val Arg Ser Gln Lys Asp Ser Lys Val Asp Leu Ile Tyr Gln
            1300                1305                1310
Asn Thr Thr Ala Met Thr Ile Tyr Glu Asn Leu Ala Pro Val Thr Thr
        1315                1320                1325
Phe Gly Lys Thr Asn Gly Tyr Ile Ala
    1330                1335
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<210> 45
<211> 122
<212> PRT
<213> Homo sapiens

<400> 45

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Lys Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu Tyr Trp Pro Ser
            20                  25                  30
Lys Gln Ala Gln Asp Tyr Gly Asp Ile Thr Val Ala Met Thr Ser Glu
        35                  40                  45
Ile Val Leu Pro Glu Trp Thr Ile Arg Asp Phe Thr Val Lys Asn Ile
    50                  55                  60
Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe Thr Ser Trp
65                  70                  75                  80
Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile Asn Phe Arg
                85                  90                  95
Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu Ser Glu Ile
            100                 105                 110
Leu Val His Cys Ser Ala Gly Ile Gly Arg
        115                 120
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<210> 46
<211> 4426
<212> DNA
<213> Mus musculus

<400> 46
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agccctgcga gtctaaggcc gcggccgctc cgcgccaggc gcgctaggct ccgcgtgtgg 180
ccgccgccgc cgctgccatg tccccgggga agcccggggc gggcgacggg ggactaggcg 240
gaccggctgg cggagaagga ggcggaggcg tcggctggag acggagacga gggcgcccgg 300
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gttctgcact ctgttcctcg aatcaccggc actttgatgc ctgactggac ctgatcatga 5640
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<210> 49
<211> 1216
<212> PRT
<213> Rattus norvegicus

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35 40 45
Val Thr Ser Pro Thr Ser Val Val Leu Thr Trp Lys His Asn Asp Ser
50 55 60
Ala Thr Ser Glu Tyr Lys Ile Asn Glu Gly Asn Thr Leu Arg Tyr Thr
65 70 75 80
Val Lys Asn Gln Thr Ser Phe Asn Ile Thr Gly Leu Ser Pro Ala Thr
85 90 95
Ser Tyr Lys Phe Ser Ile Thr Leu Gly Thr Val Asn Glu Thr Ser Gly
100 105 110
Lys Pro Thr Tyr Lys Asn Ile Thr Thr Glu Pro Trp Pro Val Ser Asp
115 120 125
Leu Gln Val Ala Tyr Ile Gly Val Thr Gln Ala Leu Leu Ala Trp Ser
130 135 140
Asn Ala Asn Gly Thr Ala Ser Tyr Arg Met Gln Ile Val Glu Leu Thr
145 150 155 160
Thr Asn Ser Ser Gly Gly Ile Ser Asp Leu Lys Pro Gly Thr His Lys
165 170 175
Ser Leu Ala Val Gln Gly Ser Asn Glu Thr Gln His Asp Leu Trp Val
180 185 190
Thr Glu Gly Val Ser Asp Pro Pro Ser Ala Arg Asp Pro Ser Leu Thr
195 200 205
Glu Val Leu Leu Thr Glu Leu Lys Pro Asp Thr Gln Tyr Lys Val Thr
210 215 220
Ile Tyr Ser Gln Ala Ala Asp Gly Thr Glu Gly Gln Pro Gly Asn Lys
225 230 235 240
Val Phe Lys Thr Asn Pro Ile Gln Val Ser Asp Ile Arg Ala Val Asn
245 250 255
Ile Ser Asp Ser Asn Met Thr Leu Thr Trp Lys Ser Asn Asn Asn Glu
260 265 270
Ser His Ala Ser Phe Thr Tyr Lys Ile Tyr Val Ala Gly Gly Ser Asp
275 280 285
Ser Ile Asn Glu Thr Val Asn Glu Thr Gln Ala Val Ile Arg Gly Leu
290 295 300
Ser Ser Ser Thr Leu Tyr Asn Ile Thr Val Leu Pro Phe Leu Gly Gln
305 310 315 320
Thr Ala Gly Ile Pro Gly Phe Leu Gln Val Tyr Thr Ser Pro Arg Pro
325 330 335
Val Ser Asp Phe Arg Val Thr Asn Val Ser Leu Arg Glu Ile Gly Leu
340 345 350

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Ala Trp Arg Ser Asn Asp Ser Glu Ser Phe Glu Ile Phe Ile Thr Gln
        355                 360                 365
Glu Gly Ser Glu Lys Arg Trp Asn Ala Ser Thr Gly Asp Leu Ser Tyr
    370                 375                 380
Ile Val Val Asn Leu Lys Pro Gly Thr Ser Tyr Gln Phe Glu Ile Phe
385                 390                 395                 400
Pro Arg Gly Pro Asn Gly Thr Glu Gly Pro Ser Gln Thr Val Val Gly
                405                 410                 415
Arg Thr Asp Cys Ser Ala Val Thr Asp Ile Arg Val Val Ser Val Ser
            420                 425                 430
Thr Thr Glu Ile Gln Leu Glu Trp Gln Asn Thr Asp Ser Ala Ser Gly
        435                 440                 445
Tyr Thr Tyr His Leu Val Leu Glu Ser Glu Asn Gly Ser Ile Lys Thr
    450                 455                 460
Asn Ser Ser Gln Lys Trp Ile Thr Val Gly Gly Leu Thr Pro Gly Thr
465                 470                 475                 480
Leu Tyr Asn Val Thr Ile Phe Pro Glu Val Asp Gln Met Glu Gly Asn
                485                 490                 495
Ser Ser Ser Ile Thr Gln Tyr Thr Arg Pro Ser Asn Val Ser Tyr Ile
            500                 505                 510
Glu Val Asn Thr Asn Thr Thr Val Gly Ala Ile Gln Trp Lys Asn Leu
        515                 520                 525
Asp Ala Ala Ser Ala Ser Tyr Ser Tyr Ser Val Leu Ile Leu Lys Ala
    530                 535                 540
Gly Asp Gly Ser Asn Val Thr Ser Arg Val Arg Asp Ile Pro Ser Val
545                 550                 555                 560
Thr Ile Pro Gly Leu Ile Pro Gly Val Ser Ser Glu Val Lys Ile Phe
                565                 570                 575
Thr Lys Ile Arg Asn Thr Glu Val Gly Asn Glu Val Pro Gly Gln Lys
            580                 585                 590
Leu Phe Cys Met Glu Pro Ala Gln Val Asp Ser Leu His Cys Glu Val
        595                 600                 605
Val Pro Lys Glu Pro Ala Leu Val Leu Lys Trp Ala Cys Pro Pro Gly
    610                 615                 620
Met Asn Ser Gly Phe Glu Leu Gly Val Arg Ser Asp Ala Trp Asp Asn
625                 630                 635                 640
Met Thr His Leu Glu Asn Cys Thr Leu Asp Asn Asp Thr Glu Cys Arg
                645                 650                 655
Thr Glu Val Thr Tyr Leu Asn Phe Ser Thr Ser Tyr Asn Ile Ser Ile
            660                 665                 670
Ala Thr Leu Ser Cys Gly Lys Met Ala Leu Pro Thr Gln Ser Thr Cys
        675                 680                 685
Thr Thr Gly Ile Thr Asp Pro Pro Pro Pro Asp Gly Ser Pro Asn Ile
    690                 695                 700
Thr Ser Val Ser His Asn Ser Val Lys Val Lys Phe Ser Gly Phe Glu
705                 710                 715                 720
Ala Ser His Gly Pro Ile Lys Ala Tyr Ala Val Leu Leu Thr Thr Gly
                725                 730                 735
Glu Ala Gly Gln Pro Ser Thr Asp Val Leu Lys Tyr Thr Tyr Glu Asp
            740                 745                 750
Phe Lys Lys Gly Ala Ser Asp Thr Tyr Val Thr Tyr Leu Ile Arg Ile
        755                 760                 765
Glu Glu Lys Gly Gln Ser Gln Gly Leu Ser Glu Ala Leu Asn Tyr Glu
    770                 775                 780
Ile Asp Val Gly Asn Gln Ser Thr Thr Leu Gly Tyr Tyr Asn Gly Arg
785                 790                 795                 800
Leu Glu Pro Leu Gly Ser Tyr Arg Ala Cys Val Ala Gly Phe Thr Asn
                805                 810                 815
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Ile Thr Tyr Asn Leu Gln Asn Asp Gly Leu Ile Asn Gly Asp Glu Ser
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Tyr Val Ser Phe Ser Pro Tyr Ser Glu Ala Val Ser Leu Pro Gln Asp
        835                 840                 845
Pro Gly Val Ile Cys Gly Ala Val Phe Gly Cys Ile Phe Gly Ala Leu
    850                 855                 860
Ala Ile Val Ala Val Gly Gly Phe Ile Phe Trp Arg Lys Lys Arg Lys
865                 870                 875                 880
Asp Ala Lys Asn Asn Glu Val Ser Phe Ser Gln Ile Lys Pro Lys Lys
                885                 890                 895
Ser Lys Leu Ile Arg Val Glu Asn Phe Glu Ala Tyr Phe Lys Lys Gln
            900                 905                 910
Gln Ala Asp Ser Asn Cys Gly Phe Ala Glu Glu Tyr Glu Asp Leu Lys
        915                 920                 925
Leu Ile Gly Ile Ser Leu Pro Lys Tyr Ala Ala Glu Ile Ala Glu Asn
    930                 935                 940
Arg Gly Lys Asn Arg Tyr Asn Asn Val Leu Pro Tyr Asp Ile Ser Arg
945                 950                 955                 960
Val Lys Leu Ser Val Gln Thr His Ser Thr Asp Asp Tyr Ile Asn Ala
                965                 970                 975
Asn Tyr Met Pro Gly Tyr His Ser Lys Lys Asp Phe Ile Ala Thr Gln
            980                 985                 990
Gly Pro Leu Pro Asn Thr Leu Lys Asp Phe Trp Arg Met Val Trp Glu
        995                 1000                1005
Lys Asn Val Tyr Ala Ile Val Met Leu Thr Lys Cys Val Glu Gln Gly
    1010                1015                1020
Arg Thr Lys Cys Glu Glu Tyr Trp Pro Ser Lys Gln Ala Gln Asp Tyr
1025                1030                1035                1040
Gly Asp Ile Thr Val Ala Met Thr Ser Glu Val Val Leu Pro Glu Trp
                1045                1050                1055
Thr Ile Arg Asp Phe Val Val Lys Asn Met Gln Ser Ser Glu Ser His
            1060                1065                1070
Pro Leu Arg Gln Phe His Phe Thr Ser Trp Pro Asp His Gly Val Pro
        1075                1080                1085
Asp Thr Thr Asp Leu Leu Ile Asn Phe Arg Tyr Leu Val Arg Asp Tyr
    1090                1095                1100
Met Lys Gln Ile Pro Pro Glu Ser Pro Ile Leu Val His Cys Ser Ala
1105                1110                1115                1120
Gly Val Gly Arg Thr Gly Thr Phe Ile Ala Ile Asp Arg Leu Ile Tyr
                1125                1130                1135
Gln Ile Glu Asn Glu Asn Thr Val Asp Val Tyr Gly Ile Val Tyr Asp
            1140                1145                1150
Leu Arg Met His Arg Pro Leu Met Val Gln Thr Glu Asp Gln Tyr Val
        1155                1160                1165
Phe Leu Asn Gln Cys Val Leu Asp Ile Ile Arg Ala Gln Lys Asp Ser
    1170                1175                1180
Lys Val Asp Leu Ile Tyr Gln Asn Thr Thr Ala Met Thr Ile Tyr Glu
1185                1190                1195                1200
Asn Leu Glu Arg Val Ser Met Phe Gly Lys Ala Asn Gly Tyr Ile Ala
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<210> 50
<211> 1785
<212> DNA
<213> Homo sapiens

<400> 50

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gaggagctgg tctatgaaaa tttctatgca gattttggac cgctgaactt ggcaatggtg 180
tacagatatt gctgcaaact aaacaagaaa ctaaaatcat acagtttgtc aagaaagaaa 240
atagtgcact acacctgttt tgaccaacgg aaaagagcaa atgcagcatt tttgataggt 300
gcctatgcag taatctattt aaagaagaca ccagaagaag cctacagagc actcctgtct 360
ggctcaaacc ccccctatct tccattcagg gatgcttcct ttggaaattg cacttacaat 420
ctcaccattc tcgactgttt gcagggaatc agaaagggat tacaacatgg atttttgac 480
tttgagacat ttgatgtgga tgaatatgaa cattatgagc gagttgaaaa tggtgacttc 540
aactggattg ttccaggaaa atttttagca tttagtggac cacatcctaa aagcaaaatt 600
gagaatggtt atcctcttca cgcccctgaa gcctactttc cttatttcaa aaagcataat 660
gtgactgcag ttgtgaggct aaacaaaaag atttatgagg caaagcgctt cacagacgct 720
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catgctgaaa taattgcttg gattagaata tgccggccag gctctattat aggaccccag 960
cagcacttcc tggaagaaaa acaagcatcg ttgtgggtcc aaggagacat tttccgatcc 1020
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gatatgtcta ttggtggaaa tctttcaaaa acacaaaaca tggaacgatt tggagaggat 1140
aacttagaag atgatgatgt ggaaatgaaa aatggtataa cccagggaga caaactacgt 1200
gccttaaaaa gtcagagaca gccacgtacc tcaccatcct gtgcatttag gtcagatgat 1260
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aacagcaacg ggggcaacct gaacagcccc ccaggccccc acagcgccaa gacagaggag 1680
cacaccacca tcctccgacc ctcctacacc gggctttctt cttcttcagc gagattcctg 1740
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<210> 51
<211> 594
<212> PRT
<213> Homo sapiens

<400> 51
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Asn Thr His Tyr Phe Ser Ile Asp Glu Glu Leu Val Tyr Glu Asn Phe
35 40 45
Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met Val Tyr Arg Tyr Cys
50 55 60
Cys Lys Leu Asn Lys Lys Leu Lys Ser Tyr Ser Leu Ser Arg Lys Lys
65 70 75 80
Ile Val His Tyr Thr Cys Phe Asp Gln Arg Lys Arg Ala Asn Ala Ala
85 90 95
Phe Leu Ile Gly Ala Tyr Ala Val Ile Tyr Leu Lys Lys Thr Pro Glu
100 105 110
Glu Ala Tyr Arg Ala Leu Leu Ser Gly Ser Asn Pro Pro Tyr Leu Pro
115 120 125
Phe Arg Asp Ala Ser Phe Gly Asn Cys Thr Tyr Asn Leu Thr Ile Leu
130 135 140
Asp Cys Leu Gln Gly Ile Arg Lys Gly Leu Gln His Gly Phe Phe Asp
145 150 155 160
Phe Glu Thr Phe Asp Val Asp Glu Tyr Glu His Tyr Glu Arg Val Glu

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                165                 170                 175
Asn Gly Asp Phe Asn Trp Ile Val Pro Gly Lys Phe Leu Ala Phe Ser
            180                 185                 190
Gly Pro His Pro Lys Ser Lys Ile Glu Asn Gly Tyr Pro Leu His Ala
        195                 200                 205
Pro Glu Ala Tyr Phe Pro Tyr Phe Lys Lys His Asn Val Thr Ala Val
    210                 215                 220
Val Arg Leu Asn Lys Lys Ile Tyr Glu Ala Lys Arg Phe Thr Asp Ala
225                 230                 235                 240
Gly Phe Glu His Tyr Asp Leu Phe Phe Ile Asp Gly Ser Thr Pro Ser
                245                 250                 255
Asp Asn Ile Val Arg Arg Phe Leu Asn Ile Cys Glu Asn Thr Glu Gly
            260                 265                 270
Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg Thr Gly Thr Leu
        275                 280                 285
Ile Ala Cys Tyr Val Met Lys His Tyr Arg Phe Thr His Ala Glu Ile
    290                 295                 300
Ile Ala Trp Ile Arg Ile Cys Arg Pro Gly Ser Ile Ile Gly Pro Gln
305                 310                 315                 320
Gln His Phe Leu Glu Glu Lys Gln Ala Ser Leu Trp Val Gln Gly Asp
                325                 330                 335
Ile Phe Arg Ser Lys Leu Lys Asn Arg Pro Ser Ser Glu Gly Ser Ile
            340                 345                 350
Asn Lys Ile Leu Ser Gly Leu Asp Asp Met Ser Ile Gly Gly Asn Leu
        355                 360                 365
Ser Lys Thr Gln Asn Met Glu Arg Phe Gly Glu Asp Asn Leu Glu Asp
    370                 375                 380
Asp Asp Val Glu Met Lys Asn Gly Ile Thr Gln Gly Asp Lys Leu Arg
385                 390                 395                 400
Ala Leu Lys Ser Gln Arg Gln Pro Arg Thr Ser Pro Ser Cys Ala Phe
                405                 410                 415
Arg Ser Asp Asp Thr Lys Gly His Pro Arg Ala Val Ser Gln Pro Phe
            420                 425                 430
Arg Leu Ser Ser Ser Leu Gln Gly Ser Ala Val Thr Leu Lys Thr Ser
        435                 440                 445
Lys Met Ala Leu Ser Pro Ser Ala Thr Ala Lys Arg Ile Asn Arg Thr
    450                 455                 460
Ser Leu Ser Ser Gly Ala Thr Val Arg Ser Phe Ser Ile Asn Ser Arg
465                 470                 475                 480
Leu Ala Ser Ser Leu Gly Asn Leu Asn Ala Ala Thr Asp Asp Pro Glu
                485                 490                 495
Asn Lys Lys Thr Ser Ser Ser Ser Lys Ala Gly Phe Thr Ala Ser Pro
            500                 505                 510
Phe Thr Asn Leu Leu Asn Gly Ser Ser Gln Pro Thr Thr Arg Asn Tyr
        515                 520                 525
Pro Glu Leu Asn Asn Asn Gln Tyr Asn Arg Ser Ser Asn Ser Asn Gly
    530                 535                 540
Gly Asn Leu Asn Ser Pro Pro Gly Pro His Ser Ala Lys Thr Glu Glu
545                 550                 555                 560
His Thr Thr Ile Leu Arg Pro Ser Tyr Thr Gly Leu Ser Ser Ser Ser
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Ala Arg Phe Leu Ser Arg Ser Ile Pro Ser Leu Gln Ser Glu Tyr Val
            580                 585                 590
His Tyr
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<210> 52

<211> 2438
<212> DNA
<213> Homo sapiens

<400> 52
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gccgggggaa gactttgccc tgccctgaga gctggtctgc gtttcccagg cgcggcggcg 180
gcggagcagc agctgcagca gccgagtcca aataggagcg gccacagcca ggggcgtgtg 240
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gaccccgaag ccgcctccgc cttcggcgcc tgctgcctcc ctcggccagg cttgttgttc 360
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gctggccacg acccagccct cccccgtgcg tatctcgctt aagatggcag cggagtcagg 480
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tagaccaaaa agcacagtaa atacccacta tttctccatc gatgaggagc tggtctatga 600
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actaaacaag aaactaaaat catacagttt gtcaagaaag aaaatagtgc actacacctg 720
ttttgaccaa cggaaaagag caaatgcagc atttttgata ggtgcctatg cagtaatcta 780
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ttcccagccg aggctgccac caaagaaatt taatagtgcc aaggaagcct tctgagcgat 2340
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<210> 53
<211> 623
<212> PRT
<213> Homo sapiens

<400> 53
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            20                  25                  30
Asn Thr His Tyr Phe Ser Ile Asp Glu Glu Leu Val Tyr Glu Asn Phe

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        35                  40                  45
Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met Val Tyr Arg Tyr Cys
    50                  55                  60
Cys Lys Leu Asn Lys Lys Leu Lys Ser Tyr Ser Leu Ser Arg Lys Lys
65                  70                  75                  80
Ile Val His Tyr Thr Cys Phe Asp Gln Arg Lys Arg Ala Asn Ala Ala
                85                  90                  95
Phe Leu Ile Gly Ala Tyr Ala Val Ile Tyr Leu Lys Lys Thr Pro Glu
            100                 105                 110
Glu Ala Tyr Arg Ala Leu Leu Ser Gly Ser Asn Pro Pro Tyr Leu Pro
        115                 120                 125
Phe Arg Asp Ala Ser Phe Gly Asn Cys Thr Tyr Asn Leu Thr Ile Leu
    130                 135                 140
Asp Cys Leu Gln Gly Ile Arg Lys Gly Leu Gln His Gly Phe Phe Asp
145                 150                 155                 160
Phe Glu Thr Phe Asp Val Asp Glu Tyr Glu His Tyr Glu Arg Val Glu
                165                 170                 175
Asn Gly Asp Phe Asn Trp Ile Val Pro Gly Lys Phe Leu Ala Phe Ser
            180                 185                 190
Gly Pro His Pro Lys Ser Lys Ile Glu Asn Gly Tyr Pro Leu His Ala
        195                 200                 205
Pro Glu Ala Tyr Phe Pro Tyr Phe Lys Lys His Asn Val Thr Ala Val
    210                 215                 220
Val Arg Leu Asn Lys Lys Ile Tyr Glu Ala Lys Arg Phe Thr Asp Ala
225                 230                 235                 240
Gly Phe Glu His Tyr Asp Leu Phe Phe Ile Asp Gly Ser Thr Pro Ser
                245                 250                 255
Asp Asn Ile Val Arg Arg Phe Leu Asn Ile Cys Glu Asn Thr Glu Gly
            260                 265                 270
Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg Thr Gly Thr Leu
        275                 280                 285
Ile Ala Cys Tyr Val Met Lys His Tyr Arg Phe Thr His Ala Glu Ile
    290                 295                 300
Ile Ala Trp Ile Arg Ile Cys Arg Pro Gly Ser Ile Ile Gly Pro Gln
305                 310                 315                 320
Gln His Phe Leu Glu Glu Lys Gln Ala Ser Leu Trp Val Gln Gly Asp
                325                 330                 335
Ile Phe Arg Ser Lys Leu Lys Asn Arg Pro Ser Ser Glu Gly Ser Ile
            340                 345                 350
Asn Lys Ile Leu Ser Gly Leu Asp Asp Met Ser Ile Gly Gly Asn Leu
        355                 360                 365
Ser Lys Thr Gln Asn Met Glu Arg Phe Gly Glu Asp Asn Leu Glu Asp
    370                 375                 380
Asp Asp Val Glu Met Lys Asn Gly Ile Thr Gln Gly Asp Lys Leu Arg
385                 390                 395                 400
Ala Leu Lys Ser Gln Arg Gln Pro Arg Thr Ser Pro Ser Cys Ala Phe
                405                 410                 415
Arg Ser Asp Asp Thr Lys Gly His Pro Arg Ala Val Ser Gln Pro Phe
            420                 425                 430
Arg Leu Ser Ser Ser Leu Gln Gly Ser Ala Val Thr Leu Lys Thr Ser
        435                 440                 445
Lys Met Ala Leu Ser Pro Ser Ala Thr Ala Lys Arg Ile Asn Arg Thr
    450                 455                 460
Ser Leu Ser Ser Gly Ala Thr Val Arg Ser Phe Ser Ile Asn Ser Arg
465                 470                 475                 480
Leu Ala Ser Ser Leu Gly Asn Leu Asn Ala Ala Thr Asp Asp Pro Glu
                485                 490                 495
Asn Lys Lys Thr Ser Ser Ser Ser Lys Ala Gly Phe Thr Ala Ser Pro
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            500                 505                 510
Phe Thr Asn Leu Leu Asn Gly Ser Ser Gln Pro Thr Thr Arg Asn Tyr
        515                 520                 525
Pro Glu Leu Asn Asn Asn Gln Tyr Asn Arg Ser Ser Asn Ser Asn Gly
    530                 535                 540
Gly Asn Leu Asn Ser Pro Pro Gly Pro His Ser Ala Lys Thr Glu Glu
545                 550                 555                 560
His Thr Thr Ile Leu Arg Pro Ser Tyr Thr Gly Leu Ser Ser Ser Ser
                565                 570                 575
Ala Arg Phe Leu Ser Arg Ser Ile Pro Val Ser Ala Gln Thr Pro Pro
            580                 585                 590
Pro Gly Pro Gln Asn Pro Glu Cys Asn Phe Cys Ala Leu Pro Ser Gln
        595                 600                 605
Pro Arg Leu Pro Pro Lys Lys Phe Asn Ser Ala Lys Glu Ala Phe
    610                 615                 620
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<210> 54
<211> 1890
<212> DNA
<213> Homo sapiens

<400> 54

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gactttgccc tgccctgaga gctggtctgc gtttcccagg cgcggcggcg gcggagcagc 180
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ccgcctccgc cttcggcgcc tgctgcctcc ctcggccagg cttgttgttc gggactgtga 360
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Glu Ala Tyr Arg Ala Leu Leu Ser Gly Ser Asn Pro Pro Tyr Leu Pro
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Pro Lys Ser Ala Ser Asn Val His Tyr Phe Ser Ile Asp Asn Glu Leu
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Glu Tyr Glu Asn Phe Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met
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Ile Ala Phe Cys Gly Pro His Ser Arg Ala Arg Leu Glu Ser Gly Tyr

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<210> 59
<211> 471
<212> PRT
<213> Homo sapiens

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35 40 45
Tyr Leu Asp Ile Thr Asp Arg Leu Cys Phe Ala Ile Leu Tyr Ser Arg
50 55 60
Pro Lys Ser Ala Ser Asn Val His Tyr Phe Ser Ile Asp Asn Glu Leu
65 70 75 80
Glu Tyr Glu Asn Phe Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met
85 90 95
Val Tyr Arg Tyr Cys Cys Lys Ile Asn Lys Lys Leu Lys Ser Ile Thr
100 105 110
Met Leu Arg Lys Lys Ile Val His Phe Thr Gly Ser Asp Gln Arg Lys
115 120 125
Gln Ala Asn Ala Ala Phe Leu Val Gly Cys Tyr Met Val Ile Tyr Leu
130 135 140
Gly Arg Thr Pro Glu Glu Ala Tyr Arg Ile Leu Ile Phe Gly Glu Thr
145 150 155 160
Ser Tyr Ile Pro Phe Arg Asp Ala Ala Tyr Gly Ser Cys Asn Phe Tyr
165 170 175
Ile Thr Leu Leu Asp Cys Phe His Ala Val Lys Lys Ala Met Gln Tyr
180 185 190
Gly Phe Leu Asn Phe Asn Ser Phe Asn Leu Asp Glu Tyr Glu His Tyr
195 200 205
Glu Lys Ala Glu Asn Gly Asp Leu Asn Trp Ile Ile Pro Asp Arg Phe
210 215 220
Ile Ala Phe Cys Gly Pro His Ser Arg Ala Arg Leu Glu Ser Gly Tyr
225 230 235 240
His Gln His Ser Pro Glu Thr Tyr Ile Gln Tyr Phe Lys Asn His Asn
245 250 255
Val Thr Thr Ile Ile Arg Leu Asn Lys Arg Met Tyr Asp Ala Lys Arg
260 265 270
Phe Thr Asp Ala Gly Phe Asp His His Asp Leu Phe Phe Ala Asp Gly
275 280 285
Ser Thr Pro Thr Asp Ala Ile Val Lys Glu Phe Leu Asp Ile Cys Glu
290 295 300
Asn Ala Glu Gly Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg
305 310 315 320
Thr Gly Thr Leu Ile Ala Cys Tyr Ile Met Lys His Tyr Arg Met Thr

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                325                 330                 335
Ala Ala Glu Thr Ile Ala Trp Val Arg Ile Cys Arg Pro Gly Ser Val
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Ile Gly Pro Gln Gln Gln Phe Leu Val Met Lys Gln Thr Asn Leu Trp
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Leu Glu Gly Asp Tyr Phe Arg Gln Lys Leu Lys Gly Gln Glu Asn Gly
    370                 375                 380
Gln His Arg Ala Ala Phe Ser Lys Leu Leu Ser Gly Val Asp Asp Ile
385                 390                 395                 400
Ser Ile Asn Gly Val Glu Asn Gln Asp Gln Gln Glu Pro Glu Pro Tyr
                405                 410                 415
Ser Asp Asp Asp Glu Ile Asn Gly Val Thr Gln Gly Asp Arg Leu Arg
            420                 425                 430
Ala Leu Lys Ser Arg Arg Gln Ser Lys Thr Asn Ala Ile Pro Leu Thr
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Asp Gly Trp Leu Ser Gln Ala Val Thr Phe Leu Asp Arg Leu Leu Ile
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Trp Leu Gly Ile His Lys Asp
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<210> 60
<211> 2646
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 2300
<223> n = A,T,C or G

<400> 60

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<211> 459
<212> PRT
<213> Homo sapiens

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35 40 45
Tyr Leu Asp Ile Thr Asp Arg Leu Cys Phe Ala Ile Leu Tyr Ser Arg
50 55 60
Pro Lys Ser Ala Ser Asn Val His Tyr Phe Ser Ile Asp Asn Glu Leu
65 70 75 80
Glu Tyr Glu Asn Phe Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met
85 90 95
Val Tyr Arg Tyr Cys Cys Lys Ile Asn Lys Lys Leu Lys Ser Ile Thr
100 105 110
Met Leu Arg Lys Lys Ile Val His Phe Thr Gly Ser Asp Gln Arg Lys
115 120 125
Gln Ala Asn Ala Ala Phe Leu Val Gly Cys Tyr Met Val Ile Tyr Leu
130 135 140
Gly Arg Thr Pro Glu Glu Ala Tyr Arg Ile Leu Ile Phe Gly Glu Thr
145 150 155 160
Ser Tyr Ile Pro Phe Arg Asp Ala Ala Tyr Gly Ser Cys Asn Phe Tyr
165 170 175
Ile Thr Leu Leu Asp Cys Phe His Ala Val Lys Lys Ala Met Gln Tyr
180 185 190
Gly Phe Leu Asn Phe Asn Ser Phe Asn Leu Asp Glu Tyr Glu His Tyr
195 200 205
Glu Lys Ala Glu Asn Gly Asp Leu Asn Trp Ile Ile Pro Asp Arg Phe
210 215 220
Ile Ala Phe Cys Gly Pro His Ser Arg Ala Arg Leu Glu Ser Gly Tyr
225 230 235 240
His Gln His Ser Pro Glu Thr Tyr Ile Gln Tyr Phe Lys Asn His Asn
245 250 255

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Val Thr Thr Ile Ile Arg Leu Asn Lys Arg Met Tyr Asp Ala Lys Arg
            260                 265                 270
Phe Thr Asp Ala Gly Phe Asp His His Asp Leu Phe Phe Ala Asp Gly
        275                 280                 285
Ser Thr Pro Thr Asp Ala Ile Val Lys Glu Phe Leu Asp Ile Cys Glu
    290                 295                 300
Asn Ala Glu Gly Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg
305                 310                 315                 320
Thr Gly Thr Leu Ile Ala Cys Tyr Ile Met Lys His Tyr Arg Met Thr
                325                 330                 335
Ala Ala Glu Thr Ile Ala Trp Val Arg Ile Cys Arg Pro Gly Ser Val
            340                 345                 350
Ile Gly Pro Gln Gln Gln Phe Leu Val Met Lys Gln Thr Asn Leu Trp
        355                 360                 365
Leu Glu Gly Asp Tyr Phe Arg Gln Lys Leu Lys Gly Gln Glu Asn Gly
    370                 375                 380
Gln His Arg Ala Ala Phe Ser Lys Leu Leu Ser Gly Val Asp Asp Ile
385                 390                 395                 400
Ser Ile Asn Gly Val Glu Asn Gln Asp Gln Gln Glu Pro Glu Pro Tyr
                405                 410                 415
Ser Asp Asp Asp Glu Ile Asn Gly Val Thr Gln Gly Asp Arg Leu Arg
            420                 425                 430
Ala Leu Lys Ser Arg Arg Gln Ser Lys Thr Asn Ala Ile Pro Leu Thr
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Leu Ser Ile Ser Arg Thr Lys Thr Val Leu Arg
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<210> 62
<211> 2160
<212> DNA
<213> Homo sapiens

<400> 62

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<210> 63
<211> 700
<212> PRT
<213> Homo sapiens

<400> 63
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Thr Thr Thr Ser Gly Pro Pro Asp Pro Gly Ala Ser Gln Pro Leu Leu
35 40 45
Ala Trp Leu Leu Leu Pro Leu Leu Leu Leu Leu Leu Val Leu Leu Leu
50 55 60
Ala Ala Tyr Phe Phe Arg Phe Arg Lys Gln Arg Lys Ala Val Val Ser
65 70 75 80
Thr Ser Asp Lys Lys Met Pro Asn Gly Ile Leu Glu Glu Gln Glu Gln
85 90 95
Gln Arg Val Met Leu Leu Ser Arg Ser Pro Ser Gly Pro Lys Lys Tyr
100 105 110
Phe Pro Ile Pro Val Glu His Leu Glu Glu Glu Ile Arg Ile Arg Ser
115 120 125
Ala Asp Asp Cys Lys Gln Phe Arg Glu Glu Phe Asn Ser Leu Pro Ser
130 135 140
Gly His Ile Gln Gly Thr Phe Glu Leu Ala Asn Lys Glu Glu Asn Arg
145 150 155 160
Glu Lys Asn Arg Tyr Pro Asn Ile Leu Pro Asn Asp His Ser Arg Val
165 170 175
Ile Leu Ser Gln Leu Asp Gly Ile Pro Cys Ser Asp Tyr Ile Asn Ala
180 185 190
Ser Tyr Ile Asp Gly Tyr Lys Glu Lys Asn Lys Phe Ile Ala Ala Gln
195 200 205
Gly Pro Lys Gln Glu Thr Val Asn Asp Phe Trp Arg Met Val Trp Glu
210 215 220
Gln Lys Ser Ala Thr Ile Val Met Leu Thr Asn Leu Lys Glu Arg Lys
225 230 235 240
Glu Glu Lys Cys His Gln Tyr Trp Pro Asp Gln Gly Cys Trp Thr Tyr
245 250 255
Gly Asn Ile Arg Val Cys Val Glu Asp Cys Val Val Leu Val Asp Tyr
260 265 270
Thr Ile Arg Lys Phe Cys Ile Gln Pro Gln Leu Pro Asp Gly Cys Lys
275 280 285
Ala Pro Arg Leu Val Ser Gln Leu His Phe Thr Ser Trp Pro Asp Phe
290 295 300

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Gly Val Pro Phe Thr Pro Ile Gly Met Leu Lys Phe Leu Lys Lys Val
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Lys Thr Leu Asn Pro Val His Ala Gly Pro Ile Val Val His Cys Ser
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Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Val Ile Asp Ala Met Met
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Ala Met Met His Ala Glu Gln Lys Val Asp Val Phe Glu Phe Val Ser
        355                 360                 365
Arg Ile Arg Asn Gln Arg Pro Gln Met Val Gln Thr Asp Met Gln Tyr
    370                 375                 380
Thr Phe Ile Tyr Gln Ala Leu Leu Glu Tyr Tyr Leu Tyr Gly Asp Thr
385                 390                 395                 400
Glu Leu Asp Val Ser Ser Leu Glu Lys His Leu Gln Thr Met His Gly
                405                 410                 415
Thr Thr Thr His Phe Asp Lys Ile Gly Leu Glu Glu Glu Phe Arg Lys
            420                 425                 430
Leu Thr Asn Val Arg Ile Met Lys Glu Asn Met Arg Thr Gly Asn Leu
        435                 440                 445
Pro Ala Asn Met Lys Lys Ala Arg Val Ile Gln Ile Ile Pro Tyr Asp
    450                 455                 460
Phe Asn Arg Val Ile Leu Ser Met Lys Arg Gly Gln Glu Tyr Thr Asp
465                 470                 475                 480
Tyr Ile Asn Ala Ser Phe Ile Asp Gly Tyr Arg Gln Lys Asp Tyr Phe
                485                 490                 495
Ile Ala Thr Gln Gly Pro Leu Ala His Thr Val Glu Asp Phe Trp Arg
            500                 505                 510
Met Ile Trp Glu Trp Lys Ser His Thr Ile Val Met Leu Thr Glu Val
        515                 520                 525
Gln Glu Arg Glu Gln Asp Lys Cys Tyr Gln Tyr Trp Pro Thr Glu Gly
    530                 535                 540
Ser Val Thr His Gly Glu Ile Thr Ile Glu Ile Lys Asn Asp Thr Leu
545                 550                 555                 560
Ser Glu Ala Ile Ser Ile Arg Asp Phe Leu Val Thr Leu Asn Gln Pro
                565                 570                 575
Gln Ala Arg Gln Glu Glu Gln Val Arg Val Val Arg Gln Phe His Phe
            580                 585                 590
His Gly Trp Pro Glu Ile Gly Ile Pro Ala Glu Gly Lys Gly Met Ile
        595                 600                 605
Asp Leu Ile Ala Ala Val Gln Lys Gln Gln Gln Gln Thr Gly Asn His
    610                 615                 620
Pro Ile Thr Val His Cys Ser Ala Gly Ala Gly Arg Thr Gly Thr Phe
625                 630                 635                 640
Ile Ala Leu Ser Asn Ile Leu Glu Arg Val Lys Ala Glu Gly Leu Leu
                645                 650                 655
Asp Val Phe Gln Ala Val Lys Ser Leu Arg Leu Gln Arg Pro His Met
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Val Gln Thr Leu Glu Gln Tyr Glu Phe Cys Tyr Lys Val Val Gln Asp
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Phe Ile Asp Ile Phe Ser Asp Tyr Ala Asn Phe Lys
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<210> 64
<211> 2827
<212> DNA
<213> Mus musculus

<220>

<221> misc_feature
<222> 63, 295, 296
<223> n = A,T,C or G

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aaaaaaa 2827

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<211> 699
<212> PRT
<213> Mus musculus

<400> 65
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35 40 45
Leu Thr Trp Leu Leu Leu Pro Leu Leu Leu Leu Leu Phe Leu Leu Ala
50 55 60
Ala Tyr Phe Phe Arg Phe Arg Lys Gln Arg Lys Ala Val Val Ser Ser
65 70 75 80
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Arg Val Met Leu Leu Ser Arg Ser Pro Ser Gly Pro Lys Lys Phe Phe
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Pro Ile Pro Val Glu His Leu Glu Glu Glu Ile Arg Val Arg Ser Ala
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Asp Asp Cys Lys Arg Phe Arg Glu Glu Phe Asn Ser Leu Pro Ser Gly
130 135 140
His Ile Gln Gly Thr Phe Glu Leu Ala Asn Lys Glu Glu Asn Arg Glu
145 150 155 160
Lys Asn Arg Tyr Pro Asn Ile Leu Pro Asn Asp His Cys Arg Val Ile
165 170 175
Leu Ser Gln Val Asp Gly Ile Pro Cys Ser Asp Tyr Ile Asn Ala Ser
180 185 190
Tyr Ile Asp Gly Tyr Lys Glu Lys Asn Lys Phe Ile Ala Ala Gln Gly
195 200 205
Pro Lys Gln Glu Thr Val Asn Asp Phe Trp Arg Met Val Trp Glu Gln
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Arg Ser Ala Thr Ile Val Met Leu Thr Asn Leu Lys Glu Arg Lys Glu
225 230 235 240
Glu Lys Cys Tyr Gln Tyr Trp Pro Asp Gln Gly Cys Trp Thr Tyr Gly
245 250 255
Asn Ile Arg Val Cys Val Glu Asp Cys Val Val Leu Val Asp Tyr Thr
260 265 270
Ile Arg Lys Phe Cys Ile His Pro Gln Leu Pro Asp Ser Cys Lys Ala
275 280 285
Pro Arg Leu Val Ser Gln Leu His Phe Thr Ser Trp Pro Asp Phe Gly
290 295 300
Val Pro Phe Thr Pro Ile Gly Met Leu Lys Phe Leu Lys Lys Val Lys
305 310 315 320
Thr Leu Asn Pro Ser His Ala Gly Pro Ile Val Val His Cys Ser Ala
325 330 335
Gly Val Gly Arg Thr Gly Thr Phe Ile Val Ile Asp Ala Met Met Asp
340 345 350
Met Ile His Ser Glu Gln Lys Val Asp Val Phe Glu Phe Val Ser Arg
355 360 365
Ile Arg Asn Gln Arg Pro Gln Met Val Gln Thr Asp Val Gln Tyr Thr
370 375 380
Phe Ile Tyr Gln Ala Leu Leu Glu Tyr Tyr Leu Tyr Gly Asp Thr Glu
385 390 395 400
Leu Asp Val Ser Ser Leu Glu Arg His Leu Gln Thr Leu His Ser Thr
405 410 415
Ala Thr His Phe Asp Lys Ile Gly Leu Glu Glu Glu Phe Arg Lys Leu
420 425 430
Thr Asn Val Arg Ile Met Lys Glu Asn Met Arg Thr Gly Asn Leu Pro
435 440 445

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Ala Asn Met Lys Lys Ala Arg Val Ile Gln Ile Ile Pro Tyr Asp Phe
    450                 455                 460
Asn Arg Val Ile Leu Ser Met Lys Arg Gly Gln Glu Phe Thr Asp Tyr
465                 470                 475                 480
Ile Asn Ala Ser Phe Ile Asp Gly Tyr Arg Gln Lys Asp Tyr Phe Met
                485                 490                 495
Ala Thr Gln Ala Pro Leu Ala His Thr Val Glu Asp Phe Trp Arg Met
            500                 505                 510
Val Trp Glu Trp Lys Ser His Thr Met Leu Met Leu Thr Glu Val Gln
        515                 520                 525
Glu Arg Glu Gln Asp Lys Cys Tyr Gln Tyr Trp Pro Thr Glu Gly Ser
    530                 535                 540
Val Thr His Gly Asp Ile Thr Ile Glu Ile Lys Ser Asp Thr Leu Ser
545                 550                 555                 560
Glu Ala Ile Ser Val Arg Asp Phe Leu Val Thr Phe Lys Gln Pro Leu
                565                 570                 575
Ala Arg Gln Glu Glu Gln Val Arg Met Val Arg Gln Phe His Phe His
            580                 585                 590
Gly Trp Pro Glu Val Gly Ile Pro Ala Glu Gly Lys Gly Met Ile Asp
        595                 600                 605
Leu Ile Ala Ala Val Gln Lys Gln Gln Gln Gln Thr Gly Asn His Pro
    610                 615                 620
Ile Thr Val His Cys Ser Ala Gly Ala Gly Arg Thr Gly Thr Phe Ile
625                 630                 635                 640
Ala Leu Ser Asn Ile Leu Glu Arg Val Lys Ala Glu Gly Leu Leu Asp
                645                 650                 655
Val Phe Gln Ala Val Lys Ser Leu Arg Leu Gln Arg Pro His Met Val
            660                 665                 670
Gln Thr Leu Glu Gln Tyr Glu Phe Cys Tyr Lys Val Val Gln Asp Phe
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Ile Asp Ile Phe Ser Asp Tyr Ala Asn Phe Lys
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<210> 66
<211> 2155
<212> DNA
<213> Rattus norvegicus

<400> 66

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caacgacaag aagatgccta acgggatcct agaagaacaa gagcagcaga gagtgatgct 180
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<210> 67
<211> 659
<212> PRT
<213> Rattus norvegicus

<400> 67

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            20                  25                  30
Gln Arg Lys Ala Val Val Asn Ser Asn Asp Lys Lys Met Pro Asn Gly
        35                  40                  45
Ile Leu Glu Glu Gln Glu Gln Gln Arg Val Met Leu Leu Ser Arg Ser
    50                  55                  60
Pro Ser Gly Pro Lys Lys Tyr Phe Pro Ile Pro Val Glu His Leu Glu
65                  70                  75                  80
Glu Glu Ile Arg Val Arg Ser Ala Asp Asp Cys Lys Arg Phe Arg Glu
                85                  90                  95
Glu Phe Asn Ser Leu Pro Ser Gly His Ile Gln Gly Thr Phe Glu Leu
            100                 105                 110
Ala Asn Lys Glu Glu Asn Arg Glu Lys Asn Arg Tyr Pro Asn Ile Leu
        115                 120                 125
Pro Asn Asp His Cys Arg Val Ile Leu Ser Gln Leu Asp Gly Ile Pro
    130                 135                 140
Cys Ser Asp Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Tyr Lys Glu Lys
145                 150                 155                 160
Asn Lys Phe Ile Ala Ala Gln Gly Pro Lys Gln Glu Thr Val Asn Asp
                165                 170                 175
Phe Trp Arg Met Val Trp Glu Gln Arg Ser Ala Thr Ile Val Met Leu
            180                 185                 190
Thr Asn Leu Lys Glu Arg Lys Glu Glu Lys Cys Tyr Gln Tyr Trp Pro
        195                 200                 205
Asp Gln Gly Cys Trp Thr Tyr Gly Asn Ile Arg Val Cys Val Glu Asp
    210                 215                 220
Cys Val Val Leu Val Asp Tyr Thr Ile Arg Lys Phe Cys Ile His Pro
225                 230                 235                 240
Gln Leu Pro Asp Ser Cys Lys Ala Pro Arg Leu Val Ser Gln Leu His
                245                 250                 255
Phe Thr Ser Trp Pro Asp Phe Gly Val Pro Phe Thr Pro Ile Gly Met
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260 265 270
Leu Lys Phe Leu Lys Lys Val Lys Thr Leu Asn Pro Ser His Ala Gly
275 280 285
Pro Ile Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe
290 295 300
Ile Val Ile Asp Ala Met Met Asp Met Ile His Ser Glu Gln Lys Val
305 310 315 320
Asp Val Phe Glu Phe Val Ser Arg Ile Arg Asn Gln Arg Pro Gln Met
325 330 335
Val Gln Thr Asp Val Gln Tyr Thr Phe Ile Tyr Gln Ala Leu Leu Glu
340 345 350
Tyr Tyr Leu Tyr Gly Asp Thr Glu Leu Asp Val Ser Ser Leu Glu Arg
355 360 365
His Leu Gln Thr Leu His Gly Thr Ala Thr His Phe Asp Lys Ile Gly
370 375 380
Leu Glu Glu Glu Phe Arg Lys Leu Thr Asn Val Arg Ile Met Lys Glu
385 390 395 400
Asn Met Arg Thr Gly Asn Leu Pro Ala Asn Met Lys Lys Ala Arg Val
405 410 415
Ile Gln Ile Ile Pro Tyr Asp Phe Asn Arg Val Ile Leu Ser Met Lys
420 425 430
Arg Gly Gln Glu Phe Thr Asp Tyr Ile Asn Ala Ser Phe Ile Asp Gly
435 440 445
Tyr Arg Gln Lys Asp Tyr Phe Met Ala Thr Gln Gly Pro Leu Ala His
450 455 460
Thr Val Glu Asp Phe Trp Arg Met Val Trp Glu Trp Lys Ser His Thr
465 470 475 480
Ile Val Met Leu Thr Glu Val Gln Glu Arg Glu Gln Asp Lys Cys Tyr
485 490 495
Gln Tyr Trp Pro Thr Glu Gly Ser Val Thr His Gly Asp Ile Thr Ile
500 505 510
Glu Ile Lys Ser Asp Thr Leu Ser Glu Ala Ile Ser Ile Arg Asp Phe
515 520 525
Leu Val Thr Phe Thr Gln Pro Leu Ala Arg Gln Glu Glu Gln Val Arg
530 535 540
Met Val Arg Gln Phe His Phe His Ala Trp Pro Glu Val Gly Ile Pro
545 550 555 560
Thr Glu Gly Lys Gly Met Ile Asp Leu Leu Ser Ala Val Gln Lys Gln
565 570 575
Gln Gln Gln Thr Asp Asn His Pro Ile Thr Val His Cys Ser Ala Gly
580 585 590
Ala Gly Arg Thr Gly Thr Phe Ile Ala Leu Ser Asn Ile Leu Glu Arg
595 600 605
Val Lys Ala Glu Gly Leu Leu Asp Val Phe Gln Ala Val Lys Ser Leu
610 615 620
Arg Leu Gln Arg Pro His Met Val Gln Thr Leu Glu Gln Tyr Glu Phe
625 630 635 640
Cys Tyr Lys Val Val Gln Asp Phe Ile Asp Ile Phe Ser Asp Tyr Ala
645 650 655
Asn Phe Lys

<210> 68
<211> 2938
<212> DNA
<213> Homo sapiens

<400> 68
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<210> 69
<211> 780
<212> PRT
<213> Homo sapiens

<400> 69
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Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
        35                  40                  45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
    50                  55                  60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys
65                  70                  75                  80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly
                85                  90                  95
Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr Gln Gly Pro Leu Ala Asn
            100                 105                 110
Thr Val Ile Asp Phe Trp Arg Met Val Trp Glu Tyr Asn Val Val Ile
        115                 120                 125
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu
    130                 135                 140
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe
145                 150                 155                 160
Lys Ile Ser Cys Glu Asp Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg
                165                 170                 175
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe
            180                 185                 190
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser
        195                 200                 205
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp
    210                 215                 220
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala
225                 230                 235                 240
Ile Cys Ala Ile Asp Tyr Thr Trp Asn Leu Leu Lys Ala Gly Lys Ile
                245                 250                 255
Pro Glu Glu Phe Asn Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln
            260                 265                 270
Arg His Ser Ala Val Gln Thr Lys Glu Gln Tyr Glu Leu Val His Arg
        275                 280                 285
Ala Ile Ala Gln Leu Phe Glu Lys Gln Leu Gln Leu Tyr Glu Ile His
    290                 295                 300
Gly Ala Gln Lys Ile Ala Asp Gly Val Asn Glu Ile Asn Thr Glu Asn
305                 310                 315                 320
Met Val Ser Ser Ile Glu Pro Glu Lys Gln Asp Ser Pro Pro Pro Lys
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Pro Pro Arg Thr Arg Ser Cys Leu Val Glu Gly Asp Ala Lys Glu Glu
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Ile Leu Gln Pro Pro Glu Pro His Pro Val Pro Pro Ile Leu Thr Pro
        355                 360                 365
Ser Pro Pro Ser Ala Phe Pro Thr Val Thr Thr Val Trp Gln Asp Asn
    370                 375                 380
Asp Arg Tyr His Pro Lys Pro Val Leu His Met Val Ser Ser Glu Gln
385                 390                 395                 400
His Ser Ala Asp Leu Asn Arg Asn Tyr Ser Lys Ser Thr Glu Leu Pro
                405                 410                 415
Gly Lys Asn Glu Ser Thr Ile Glu Gln Ile Asp Lys Lys Leu Glu Arg
            420                 425                 430
Asn Leu Ser Phe Glu Ile Lys Lys Val Pro Leu Gln Glu Gly Pro Lys
        435                 440                 445
Ser Phe Asp Gly Asn Thr Leu Leu Asn Arg Gly His Ala Ile Lys Ile
    450                 455                 460
Lys Ser Ala Ser Pro Cys Ile Ala Asp Lys Ile Ser Lys Pro Gln Glu
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465                 470                 475                 480
Leu Ser Ser Asp Leu Asn Val Gly Asp Thr Ser Gln Asn Ser Cys Val
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Glu Ser Gln Asn Ser Asp Thr Pro Pro Arg Pro Asp Arg Leu Pro Leu
        515                 520                 525
Asp Glu Lys Gly His Val Thr Trp Ser Phe His Gly Pro Glu Asn Ala
    530                 535                 540
Ile Pro Ile Pro Asp Leu Ser Glu Gly Asn Ser Ser Asp Ile Asn Tyr
545                 550                 555                 560
Gln Thr Arg Lys Thr Val Ser Leu Thr Pro Ser Pro Thr Thr Gln Val
                565                 570                 575
Glu Thr Pro Asp Leu Val Asp His Asp Asn Thr Ser Pro Leu Phe Arg
            580                 585                 590
Thr Pro Leu Ser Phe Thr Asn Pro Leu His Ser Asp Asp Ser Asp Ser
        595                 600                 605
Asp Glu Arg Asn Ser Asp Gly Ala Val Thr Gln Asn Lys Thr Asn Ile
    610                 615                 620
Ser Thr Ala Ser Ala Thr Val Ser Ala Ala Thr Ser Thr Glu Ser Ile
625                 630                 635                 640
Ser Thr Arg Lys Val Leu Pro Met Ser Ile Ala Arg His Asn Ile Ala
                645                 650                 655
Gly Thr Thr His Ser Gly Ala Glu Lys Asp Val Asp Val Ser Glu Asp
            660                 665                 670
Ser Pro Pro Pro Leu Pro Glu Arg Thr Pro Glu Ser Phe Val Leu Ala
        675                 680                 685
Ser Glu His Asn Thr Pro Val Arg Ser Glu Trp Ser Glu Leu Gln Ser
    690                 695                 700
Gln Glu Arg Ser Glu Gln Lys Lys Ser Glu Gly Leu Ile Thr Ser Glu
705                 710                 715                 720
Asn Glu Lys Cys Asp His Pro Ala Gly Gly Ile His Tyr Glu Met Cys
                725                 730                 735
Ile Glu Cys Pro Pro Thr Phe Ser Asp Lys Arg Glu Gln Ile Ser Glu
            740                 745                 750
Asn Pro Thr Glu Ala Thr Asp Ile Gly Phe Gly Asn Arg Cys Gly Lys
        755                 760                 765
Pro Lys Gly Pro Arg Asp Pro Pro Ser Glu Trp Thr
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<210> 70
<211> 3160
<212> DNA
<213> Homo sapiens

<400> 70

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ctagacataa tatagcagga acaacacatt caggtgctga aaaagatgtt gatgttagtg 2040
aagattcacc tcctccccta cctgaaagaa ctcctgaatc gtttgtgtta gcaagtgaac 2100
ataatacacc tgtaagatcg gaatggagtg aacttcaaag tcaggaacga tctgaacaaa 2160
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ctttaatatt tgaactcaag tgggattaga agactatcaa aatacatgta tgtttcagat 3120
atttgacctg tcattaaaaa aaacaaacag ttttacagtg 3160

<210> 71
<211> 780
<212> PRT
<213> Homo sapiens

<400> 71
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 1  .  5  10  15
Met Lys Ser Pro Asp His Asn Gly Glu Asp Asn Phe Ala Arg Asp Phe
 20  25  30
Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
 35  40  45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
 50  55  60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys

65 70 75 80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly
85 90 95
Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr Gln Gly Pro Leu Ala Asn
100 105 110
Thr Val Ile Asp Phe Trp Arg Met Ile Trp Glu Tyr Asn Val Val Ile
115 120 125
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu
130 135 140
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe
145 150 155 160
Lys Ile Ser Cys Glu Asp Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg
165 170 175
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe
180 185 190
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser
195 200 205
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp
210 215 220
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala
225 230 235 240
Ile Cys Ala Ile Asp Tyr Thr Trp Asn Leu Leu Lys Ala Gly Lys Ile
245 250 255
Pro Glu Glu Phe Asn Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln
260 265 270
Arg His Ser Ala Val Gln Thr Lys Glu Gln Tyr Glu Leu Val His Arg
275 280 285
Ala Ile Ala Gln Leu Phe Glu Lys Gln Leu Gln Leu Tyr Glu Ile His
290 295 300
Gly Ala Gln Lys Ile Ala Asp Gly Val Asn Glu Ile Asn Thr Glu Asn
305 310 315 320
Met Ile Ser Ser Ile Glu Pro Glu Lys Gln Asp Ser Pro Pro Pro Lys
325 330 335
Pro Pro Arg Thr Arg Ser Cys Leu Val Glu Gly Asp Ala Lys Glu Glu
340 345 350
Ile Leu Gln Pro Pro Glu Pro His Pro Val Pro Pro Ile Leu Thr Pro
355 360 365
Ser Pro Pro Ser Ala Phe Pro Thr Val Thr Thr Val Trp Gln Asp Asn
370 375 380
Asp Arg Tyr His Pro Lys Pro Val Leu His Met Val Ser Ser Glu Gln
385 390 395 400
His Ser Ala Asp Leu Asn Arg Asn Tyr Ser Lys Ser Thr Glu Leu Pro
405 410 415
Gly Lys Asn Glu Ser Thr Ile Glu Gln Ile Asp Lys Lys Leu Glu Arg
420 425 430
Asn Leu Ser Phe Glu Ile Lys Lys Val Pro Leu Gln Glu Gly Pro Lys
435 440 445
Ser Phe Asp Gly Asn Thr Leu Leu Asn Arg Gly His Ala Ile Lys Ile
450 455 460
Lys Ser Ala Ser Pro Cys Ile Ala Asp Lys Ile Ser Lys Pro Gln Glu
465 470 475 480
Leu Ser Ser Asp Leu Asn Val Gly Asp Thr Ser Gln Asn Ser Cys Val
485 490 495
Asp Cys Ser Val Thr Gln Ser Asn Lys Val Ser Val Thr Pro Pro Glu
500 505 510
Glu Ser Gln Asn Ser Asp Thr Pro Pro Arg Pro Asp Arg Leu Pro Leu
515 520 525
Asp Glu Lys Gly His Val Thr Trp Ser Phe His Gly Pro Glu Asn Ala

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    530                 535                 540
Ile Pro Ile Pro Asp Leu Ser Glu Gly Asn Ser Ser Asp Ile Asn Tyr
545                 550                 555                 560
Gln Thr Arg Lys Thr Val Ser Leu Thr Pro Ser Pro Thr Thr Gln Val
                565                 570                 575
Glu Thr Pro Asp Leu Val Asp His Asp Asn Thr Ser Pro Leu Phe Arg
            580                 585                 590
Thr Pro Leu Ser Phe Thr Asn Pro Leu His Ser Asp Asp Ser Asp Ser
        595                 600                 605
Asp Glu Arg Asn Ser Asp Gly Ala Val Thr Gln Asn Lys Thr Asn Ile
    610                 615                 620
Ser Thr Ala Ser Ala Thr Val Ser Ala Ala Thr Ser Thr Glu Ser Ile
625                 630                 635                 640
Ser Thr Arg Lys Val Leu Pro Met Ser Ile Ala Arg His Asn Ile Ala
                645                 650                 655
Gly Thr Thr His Ser Gly Ala Glu Lys Asp Val Asp Val Ser Glu Asp
            660                 665                 670
Ser Pro Pro Pro Leu Pro Glu Arg Thr Pro Glu Ser Phe Val Leu Ala
        675                 680                 685
Ser Glu His Asn Thr Pro Val Arg Ser Glu Trp Ser Glu Leu Gln Ser
    690                 695                 700
Gln Glu Arg Ser Glu Gln Lys Lys Ser Glu Gly Leu Ile Thr Ser Glu
705                 710                 715                 720
Asn Glu Lys Cys Asp His Pro Ala Gly Gly Ile His Tyr Glu Met Cys
                725                 730                 735
Ile Glu Cys Pro Pro Thr Phe Ser Asp Lys Arg Glu Gln Ile Ser Glu
            740                 745                 750
Asn Pro Thr Glu Ala Thr Asp Ile Gly Phe Gly Asn Arg Cys Gly Lys
        755                 760                 765
Pro Lys Gly Pro Arg Asp Pro Pro Ser Glu Trp Thr
    770                 775                 780
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<210> 72
<211> 236
<212> DNA
<213> Homo sapiens

<400> 72
gttaaaagga acagatacaa ggacatactg ccatttgatc acagccgagt taaattgaca 60
ttaaagactc cttcacaaga ttcagactat atcaatgcaa attttataaa gggcgtctat 120
gggccaaaag catatgtagc aactcaagga cctttagcaa atacagtaat agatttttgg 180
aggatggtat gggagtataa tgttgtgatc attgtaatgg cctgccgaga atttga 236

<210> 73
<211> 78
<212> PRT
<213> Homo sapiens

<400> 73

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Val Lys Arg Asn Arg Tyr Lys Asp Ile Leu Pro Phe Asp His Ser Arg
 1               5                  10                  15
Val Lys Leu Thr Leu Lys Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn
            20                  25                  30
Ala Asn Phe Ile Lys Gly Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr
        35                  40                  45
Gln Gly Pro Leu Ala Asn Thr Val Ile Asp Phe Trp Arg Met Val Trp
    50                  55                  60
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Glu Tyr Asn Val Val Ile Ile Val Met Ala Cys Arg Glu Phe
65 70 75

<210> 74
<211> 2676
<212> DNA
<213> Mus musculus

<400> 74
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tgggggcggc acgagttgga cttccagatc ttgaactcct ttggaggctc ctccggcgct 120
ttcaccacat gccgctccca gtcgatctgc ttgttcgcct cgtagtaggg gaaagcgacg 180
ctgctcttta agttgcgcgg ggagcccggc cggtgccgcc gcagccgcag ccgcctgcgc 240
ggcggggagg gagggcgggc cggagcgagc tggggaagac ggagcgggcg ctgcggcgcg 300
cgggcgggcg gcgggggga cgcgggagga tggagcaagt ggagatcctg aggaggttca 360
tccagagggt ccaggccatg aagagtccgg atcacaatgg ggaggacaac ttcgcccggg 420
acttcatgcg attgagaaga ttgtctacca aatatagaac agaaaagatt tatcccacag 480
ccactggaga aaaagaagaa aatgttaaaa agaacagata taaggacata ctgccatttg 540
atcacagccg agttaagttg actttgaaga ctccatccca agattcagat tatatcaatg 600
caaattttat taagggtgtg tatgggccaa aagcatatgt ggcaacccaa gggcctttcc 660
ggaatacagt catagacttc tggaggatga tatgggagta taatgttgtg atgatcgtga 720
tggcctgtcg agaatttgag atgggaagga aaaagtgtga gcgctactgg cctttgtatg 780
gagaagatcc tataacattt gcaccattta aaatttcttg tgaaaatgaa caagcaagaa 840
ccgactactt catccgaaca cttttacttg aatttcaaaa tgaatcccgt cggctctatc 900
agtttcatta cgtgaactgg ccagaccatg atgttccttc gtcatttgat tctattctgg 960
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gcagtgcagg ctgtggacga acaggtgcta tttgtgccat agattacacg tggaacttac 1080
tgaaagcagg gaaaattcca gaggaattta atgtatttaa tttaatacaa gaaatgagaa 1140
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ctcaactgtt tgaaaaacag ctacaactgt atgaaattca tggagcacag aagatccgtg 1260
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tgaaagctcc cctcagcttt accaaccctc ttcactctga cgactggcac tcagacggag 2160
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ctgtaagacc tgagtggcat gaacttccaa atcaggagtg gtctgaacaa agggaatctg 2460
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ctgcagactc tccacctgct ttcagtgaca agaaagatca aataacaaaa agtccagcag 2580
aagtcacaga tattggtttt ggtaatcgct gtggaaaacc taaaggacca agagagccac 2640
cttcagaatg gacatgatgc agggagtgaa aggaca 2676

<210> 75
<211> 775

<212> PRT
<213> Mus musculus

<400> 75

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Met Glu Gln Val Glu Ile Leu Arg Arg Phe Ile Gln Arg Val Gln Ala
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            20                  25                  30
Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
        35                  40                  45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
    50                  55                  60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys
65                  70                  75                  80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly
                85                  90                  95
Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr Gln Gly Pro Phe Arg Asn
            100                 105                 110
Thr Val Ile Asp Phe Trp Arg Met Ile Trp Glu Tyr Asn Val Val Met
        115                 120                 125
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu
    130                 135                 140
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe
145                 150                 155                 160
Lys Ile Ser Cys Glu Asn Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg
                165                 170                 175
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe
            180                 185                 190
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser
        195                 200                 205
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp
    210                 215                 220
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala
225                 230                 235                 240
Ile Cys Ala Ile Asp Tyr Thr Trp Asn Leu Leu Lys Ala Gly Lys Ile
                245                 250                 255
Pro Glu Glu Phe Asn Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln
            260                 265                 270
Arg His Ser Ala Val Gln Thr Lys Glu Gln Tyr Glu Leu Val His Arg
        275                 280                 285
Ala Ile Ala Gln Leu Phe Glu Lys Gln Leu Gln Leu Tyr Glu Ile His
    290                 295                 300
Gly Ala Gln Lys Ile Arg Asp Gly Asn Glu Ile Thr Thr Gly Thr Met
305                 310                 315                 320
Val Ser Ser Ile Asp Ser Glu Lys Gln Asp Ser Pro Pro Pro Lys Pro
                325                 330                 335
Pro Arg Thr Arg Ser Cys Leu Val Glu Gly Asp Ala Lys Glu Glu Ile
            340                 345                 350
Leu Gln Pro Pro Glu Pro His Pro Val Pro Pro Ile Leu Thr Pro Ser
        355                 360                 365
Pro Pro Ser Ala Phe Pro Thr Val Thr Thr Val Trp Gln Asp Ser Asp
    370                 375                 380
Arg Tyr His Pro Lys Pro Val Leu His Met Ala Ser Pro Glu Gln His
385                 390                 395                 400
Pro Ala Asp Leu Asn Arg Ser Tyr Asp Lys Ser Ala Asp Gln Trp Gly
                405                 410                 415
Lys Ser Glu Ser Ala Ile Glu His Ile Asp Lys Lys Leu Glu Arg Asn
            420                 425                 430
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Leu Ser Phe Glu Ile Lys Lys Val Pro Leu Gln Glu Gly Pro Lys Ser
        435                 440                 445
Phe Asp Gly Asn Thr Leu Leu Asn Arg Gly His Ala Ile Lys Ile Lys
    450                 455                 460
Ser Ala Ser Ser Ser Val Val Asp Arg Thr Ser Lys Pro Gln Glu Leu
465                 470                 475                 480
Ser Ala Gly Ala Leu Lys Val Asp Asp Val Ser Gln Asn Ser Cys Ala
                485                 490                 495
Asp Cys Ser Ala Ala His Ser His Arg Ala Ala Glu Ser Ser Glu Glu
            500                 505                 510
Ser Gln Ser Asn Ser His Thr Pro Pro Arg Pro Asp Cys Leu Pro Leu
        515                 520                 525
Asp Lys Lys Gly His Val Thr Trp Ser Leu His Gly Pro Glu Asn Ala
    530                 535                 540
Thr Pro Val Pro Asp Ser Pro Asp Gly Lys Ser Pro Asp Asn His Ser
545                 550                 555                 560
Gln Thr Leu Lys Thr Val Ser Ser Thr Pro Asn Ser Thr Ala Glu Glu
                565                 570                 575
Glu Ala His Asp Leu Thr Glu His His Asn Ser Ser Pro Leu Leu Lys
            580                 585                 590
Ala Pro Leu Ser Phe Thr Asn Pro Leu His Ser Asp Asp Trp His Ser
        595                 600                 605
Asp Gly Gly Ser Ser Asp Gly Ala Val Thr Arg Asn Lys Thr Ser Ile
    610                 615                 620
Ser Thr Ala Ser Ala Thr Val Ser Pro Ala Ser Ser Ala Glu Ser Ala
625                 630                 635                 640
Cys His Arg Arg Val Leu Pro Met Ser Ile Ala Arg Gln Glu Val Ala
                645                 650                 655
Gly Thr Pro His Ser Gly Ala Glu Lys Asp Ala Asp Val Ser Glu Glu
            660                 665                 670
Ser Pro Pro Pro Leu Pro Glu Arg Thr Pro Glu Ser Phe Val Leu Ala
        675                 680                 685
Asp Met Pro Val Arg Pro Glu Trp His Glu Leu Pro Asn Gln Glu Trp
    690                 695                 700
Ser Glu Gln Arg Glu Ser Glu Gly Leu Thr Thr Ser Gly Asn Glu Lys
705                 710                 715                 720
His Asp Ala Gly Gly Ile His Thr Glu Ala Ser Ala Asp Ser Pro Pro
                725                 730                 735
Ala Phe Ser Asp Lys Lys Asp Gln Ile Thr Lys Ser Pro Ala Glu Val
            740                 745                 750
Thr Asp Ile Gly Phe Gly Asn Arg Cys Gly Lys Pro Lys Gly Pro Arg
        755                 760                 765
Glu Pro Pro Ser Glu Trp Thr
    770                 775
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<210> 76
<211> 1608
<212> DNA
<213> Rattus norvegicus

<400> 76
ccggccggtg ccgctggcag ccgctagccg cctcgctgct ggcggtggta gggtagggcg 60
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ggggacgcgg gaggatggag caagtggaga ttctgaggag gttcatccag agggtccagg 180
ccatgaaaag tccggaccac aatggggagg acaacttcgc ccgggacttc atgcgattga 240
gaagattgtc taccaaatat agaacagaaa agatttatcc cacagccact ggagaaaaag 300
aagaaaatgt taaaaagaac agatataagg acatactgcc atttgatcac agccgagtta 360

agttgacttt gaagacacca tcccaagatt cagattatat caatgcaaat tttattaagg 420
gtgtatatgg gccgagagca tacgtggcaa cccaagggcc tttggcgaat acagtcatag 480
acttctggag gatgatatgg gagtacaatg tggtgatcat tgtaatggcc tgtcgtgaat 540
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catttgcacc atttaaaatt tcttgtgaaa atgaacaagc aagaacagac tacttcattc 660
gaacactttt acttgaattt caaaatgaat cccgtcgact ctatcagttt cattacgtga 720
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cagtacaaac gaaggagcag tatgaactcg tccatagagc tattgcccaa ctgtttgaaa 1020
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gcactggaaa catggtcagt tccattgata gtgaaaaaca agattctcct cctccaaagc 1140
caccacggac tcgaagttgt cttgtagagg gggatgccaa ggaagaaatc ctccagccac 1200
cagagcctca cccggtgccg cccatcctga caccgtcgcc tccttcagca ttcccaacgt 1260
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agaagcgaat ctgctgttga gcacacagat aaaaagttag aacaaaattt aagttttgag 1440
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aggggacatg cgattaaaat taagtctgct tcatcttctg tagttgacaa aagctctaag 1560
ccacaggagt taagttcagg tgatctaaag gttcacgatg tgtctcag 1608

<210> 77
<211> 382
<212> PRT
<213> Rattus norvegicus

<400> 77
Met Glu Gln Val Glu Ile Leu Arg Arg Phe Ile Gln Arg Val Gln Ala
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Met Lys Ser Pro Asp His Asn Gly Glu Asp Asn Phe Ala Arg Asp Phe
20 25 30
Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
35 40 45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
50 55 60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys
65 70 75 80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly
85 90 95
Val Tyr Gly Pro Arg Ala Tyr Val Ala Thr Gln Gly Pro Leu Ala Asn
100 105 110
Thr Val Ile Asp Phe Trp Arg Met Ile Trp Glu Tyr Asn Val Val Ile
115 120 125
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu
130 135 140
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe
145 150 155 160
Lys Ile Ser Cys Glu Asn Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg
165 170 175
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe
180 185 190
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser
195 200 205
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp
210 215 220
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala
225 230 235 240

```
Ile Cys Ala Ile Asp Tyr Thr Trp Asn Leu Leu Lys Ala Gly Lys Ile
                245                 250                 255
Pro Glu Glu Phe Asn Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln
            260                 265                 270
Arg His Ser Ala Val Gln Thr Lys Glu Gln Tyr Glu Leu Val His Arg
        275                 280                 285
Ala Ile Ala Gln Leu Phe Glu Lys Gln Leu Gln Leu Tyr Glu Ile His
    290                 295                 300
Gly Ala Gln Lys Ile Thr Asp Gly Asn Glu Ile Ser Thr Gly Asn Met
305                 310                 315                 320
Val Ser Ser Ile Asp Ser Glu Lys Gln Asp Ser Pro Pro Pro Lys Pro
                325                 330                 335
Pro Arg Thr Arg Ser Cys Leu Val Glu Gly Asp Ala Lys Glu Glu Ile
            340                 345                 350
Leu Gln Pro Pro Glu Pro His Pro Val Pro Pro Ile Leu Thr Pro Ser
        355                 360                 365
Pro Pro Ser Ala Phe Pro Thr Leu His Cys Val Ala Arg Gln
    370                 375                 380
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<210> 78
<211> 4315
<212> DNA
<213> Homo sapiens

<400> 78

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ttgcctttct ggacacagaa gtatttgtga cagggcaaag cccaacacct tcccccactg 180
gattgactac agcaaagatg cccagtgttc cactttcaag tgacccctta cctactcaca 240
ccactgcatt ctcacccgca agcacctttg aaagagaaaa tgacttctca gagaccacaa 300
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Asp Val Pro Gly Glu Arg Ser Thr Ala Ser Thr Phe Pro Thr Asp Pro
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Val Ser Pro Leu Thr Thr Thr Leu Ser Leu Ala His His Ser Ser Ala
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Ala Leu Pro Ala Arg Thr Ser Asn Thr Thr Ile Thr Ala Asn Thr Ser
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Asp Ala Tyr Leu Asn Ala Ser Glu Thr Thr Thr Leu Ser Pro Ser Gly
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Ser Ala Val Ile Ser Thr Thr Thr Ile Ala Thr Thr Pro Ser Lys Pro
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Thr Cys Asp Glu Lys Tyr Ala Asn Ile Thr Val Asp Tyr Leu Tyr Asn
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Lys Glu Thr Lys Leu Phe Thr Ala Lys Leu Asn Val Asn Glu Asn Val
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Glu Cys Gly Asn Asn Thr Cys Thr Asn Asn Glu Val His Asn Leu Thr
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Glu Cys Lys Asn Ala Ser Val Ser Ile Ser His Asn Ser Cys Thr Ala
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Pro Asp Lys Thr Leu Ile Leu Asp Val Pro Pro Gly Val Glu Lys Phe
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Gln Leu His Asp Cys Thr Gln Val Glu Lys Ala Asp Thr Thr Ile Cys
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Leu Lys Trp Lys Asn Ile Glu Thr Phe Thr Cys Asp Thr Gln Asn Ile
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Thr Tyr Arg Phe Gln Cys Gly Asn Met Ile Phe Asp Asn Lys Glu Ile
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Ile Leu Tyr Asn Asn His Lys Phe Thr Asn Ala Ser Lys Ile Ile Lys
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Thr Asp Phe Gly Ser Pro Gly Glu Pro Gln Ile Ile Phe Cys Arg Ser
385                 390                 395                 400
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Phe His Asn Phe Thr Leu Cys Tyr Ile Lys Glu Thr Glu Lys Asp Cys
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Leu Asn Leu Asp Lys Asn Leu Ile Lys Tyr Asp Leu Gln Asn Leu Lys
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Pro Tyr Thr Lys Tyr Val Leu Ser Leu His Ala Tyr Ile Ile Ala Lys
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Val Gln Arg Asn Gly Ser Ala Ala Met Cys His Phe Thr Thr Lys Ser
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Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys Gln
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Leu Met Asn Val Glu Pro Ile His Ala Asp Ile Leu Leu Glu Thr Tyr
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Lys Arg Lys Ile Ala Asp Glu Gly Arg Pro Phe Leu Ala Glu Phe Gln
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Ser Ile Pro Arg Val Phe Ser Lys Phe Pro Ile Lys Glu Ala Arg Lys
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Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys Tyr
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Met Ile Trp Glu Gln Lys Ala Thr Val Ile Val Met Val Thr Arg Cys
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Glu Glu Gly Asn Arg Asn Lys Cys Ala Glu Tyr Trp Pro Ser Met Glu
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Lys Arg Cys Pro Asp Tyr Ile Ile Gln Lys Leu Asn Ile Val Asn Lys
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Phe Gly Glu Thr Glu Val Asn Leu Ser Glu Leu His Pro Tyr Leu His
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Glu Phe Gln Arg Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile
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Gly Asn Gln Glu Glu Asn Lys Ser Lys Asn Arg Asn Ser Asn Val Ile
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Pro Tyr Asp Tyr Asn Arg Val Pro Leu Lys His Glu Leu Glu Met Ser
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Lys Glu Ser Glu His Asp Ser Asp Glu Ser Ser Asp Asp Asp Ser Asp
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Ser Glu Glu Pro Ser Lys Tyr Ile Asn Ala Ser Phe Ile Met Ser Tyr
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Cys Gly Asn Asn Thr Cys Thr Asn Asn Glu Val His Asn Leu Thr Glu
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Cys Lys Asn Ala Ser Val Ser Ile Ser His Asn Ser Cys Thr Ala Pro
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Tyr Arg Phe Gln Cys Gly Asn Met Ile Phe Asp Asn Lys Glu Ile Lys
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Pro Pro Ser Gln Val Trp Asn Met Thr Val Ser Met Thr Ser Asp Asn
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Glu Arg Tyr His Leu Glu Val Glu Ala Gly Asn Thr Leu Val Arg Asn

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Ile Asn Ala Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys Tyr Ile
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Glu Gly Asn Arg Asn Lys Cys Ala Glu Tyr Trp Pro Ser Met Glu Glu
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Gly Thr Arg Ala Phe Gly Asp Val Val Val Lys Ile Asn Gln His Lys
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Glu Lys Ala Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr Ser Trp
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Pro Asp His Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys Leu Arg
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Arg Arg Val Asn Ala Phe Ser Asn Phe Phe Ser Gly Pro Ile Val Val
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His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile Asp
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Ala Met Leu Glu Gly Leu Glu Ala Glu Asn Lys Val Asp Val Tyr Gly
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Ala Gln Tyr Ile Leu Ile His Gln Ala Leu Val Glu Tyr Asn Gln Phe
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Met Lys Lys Arg Asp Pro Pro Ser Glu Pro Ser Pro Leu Glu Ala Glu
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Phe Gln Arg Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile Gly
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<400> 83

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| Thr | Glu | Val | Phe | Val | Thr | Gly | Gln | Thr | Pro | Thr | Pro | Ser | Asp | Glu | Leu |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Ser | Thr | Thr | Glu | Asn | Ala | Leu | Leu | Leu | Pro | Gln | Ser | Asp | Pro | Leu | Pro |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Ala | Arg | Thr | Thr | Glu | Ser | Thr | Pro | Pro | Ser | Ile | Ser | Glu | Arg | Gly | Asn |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Gly | Ser | Ser | Glu | Thr | Thr | Tyr | His | Pro | Gly | Val | Leu | Ser | Thr | Leu | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Pro | His | Leu | Ser | Pro | Gln | Pro | Asp | Ser | Gln | Thr | Pro | Ser | Ala | Gly | Gly |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Ala | Asp | Thr | Gln | Thr | Phe | Ser | Ser | Gln | Ala | Asp | Asn | Pro | Thr | Leu | Thr |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Pro | Ala | Pro | Gly | Gly | Gly | Thr | Asp | Pro | Pro | Gly | Val | Pro | Gly | Glu | Arg |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Thr | Val | Pro | Gly | Thr | Ile | Pro | Ala | Asp | Thr | Ala | Phe | Pro | Val | Asp | Thr |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Pro | Ser | Leu | Ala | Arg | Asn | Ser | Ser | Ala | Ala | Ser | Pro | Thr | His | Thr | Ser |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Asn | Val | Ser | Thr | Thr | Asp | Ile | Ser | Ser | Gly | Ala | Ser | Leu | Thr | Thr | Leu |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Thr | Pro | Ser | Thr | Leu | Gly | Leu | Ala | Ser | Thr | Asp | Pro | Pro | Ser | Thr | Thr |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Ile | Ala | Thr | Thr | Thr | Lys | Gln | Thr | Cys | Ala | Ala | Met | Phe | Gly | Asn | Ile |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Thr | Val | Asn | Tyr | Thr | Tyr | Glu | Ser | Ser | Asn | Gln | Thr | Phe | Lys | Ala | Asp |
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| Leu | Lys | Asp | Val | Gln | Asn | Ala | Lys | Cys | Gly | Asn | Glu | Asp | Cys | Glu | Asn |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Val | Leu | Asn | Asn | Leu | Glu | Glu | Cys | Ser | Gln | Ile | Lys | Asn | Ile | Ser | Val |
| | | | | 245 | | | | | 250 | | | | | 255 | |

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Ala Asn Thr Ser Ile Cys Leu Glu Trp Lys Thr Glu Asn Leu Asp Phe
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Arg Lys Cys Asn Ser Asp Asn Ile Ser Tyr Val Leu His Cys Glu Pro
305                 310                 315                 320
Glu Asn Asn Thr Lys Cys Ile Arg Arg Asn Thr Phe Ile Pro Glu Arg
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Cys Gln Leu Asp Asn Leu Arg Ala Gln Thr Asn Tyr Thr Cys Val Ala
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Glu Ile Leu Tyr Arg Gly Val Lys Leu Val Lys Asn Val Ile Asn Val
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Gln Thr Asp Leu Gly Ile Pro Glu Thr Pro Lys Pro Ser Cys Gly Asp
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Pro Ala Ala Arg Lys Thr Leu Val Ser Trp Pro Glu Pro Ala Ser Lys
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Pro Asp Pro Ala Ser Lys Pro His Gly Tyr Val Leu Cys Tyr Lys Asn
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Asn Ser Glu Lys Cys Lys Ser Leu Pro Asn Asn Val Thr Ser Phe Glu
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Val Glu Ser Leu Lys Pro Tyr Lys Tyr Tyr Glu Val Ser Leu Leu Ala
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Phe His Thr Lys Ala Asp Arg Pro Asp Lys Val Thr Gly Met Lys Thr
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Ser Arg Pro Thr Asp Asn Ser Ile Asn Val Thr Cys Gly Pro Pro Tyr
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Thr Ser Ile Ala Leu Leu Val Val Leu Tyr Lys Ile Tyr Asp Leu Arg
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Lys Lys Arg Ser Ser Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg
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755 760 765
Thr Ile Asn Asp His Lys Arg Cys Pro Asp Tyr Ile Ile Gln Lys Leu
770 775 780
Asn Val Ala His Lys Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His
785 790 795 800
Ile Gln Phe Thr Ser Trp Pro Asp His Gly Val Pro Glu Asp Pro His
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<212> PRT
<213> Rattus norvegicus

<400> 85

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| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Leu | Thr | Val | Arg | Thr | Asn | Tyr | Thr | Cys | Ala | Ala | Glu | Val | Leu | Tyr | Asn |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Asn | Val | Ile | Leu | Leu | Lys | Gln | Asp | Arg | Arg | Val | Gln | Thr | Asp | Phe | Gly |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Thr | Pro | Glu | Met | Leu | Pro | His | Val | Gln | Cys | Lys | Asn | Ser | Thr | Asn | Ser |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Thr | Thr | Leu | Val | Ser | Trp | Ala | Glu | Pro | Ala | Ser | Lys | His | His | Gly | Tyr |
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| Ile | Leu | Cys | Tyr | Lys | Lys | Thr | Pro | Ser | Glu | Lys | Cys | Glu | Asn | Leu | Ala |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Asn | Asp | Val | Asn | Ser | Phe | Glu | Val | Lys | Asn | Leu | Arg | Pro | Tyr | Thr | Glu |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Tyr | Thr | Val | Ser | Leu | Phe | Ala | Tyr | Val | Ile | Gly | Arg | Val | Gln | Arg | Asn |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Gly | Pro | Ala | Lys | Asp | Cys | Asn | Phe | Arg | Thr | Lys | Ala | Ala | Arg | Pro | Gly |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Lys | Val | Asn | Gly | Met | Lys | Thr | Ser | Arg | Ala | Ser | Asp | Asn | Ser | Ile | Asn |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Val | Thr | Cys | Asn | Ser | Pro | Tyr | Glu | Ile | Asn | Gly | Pro | Glu | Ala | Arg | Tyr |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Ile | Leu | Glu | Val | Lys | Ser | Gly | Gly | Ser | Leu | Val | Lys | Thr | Phe | Asn | Gln |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Ser | Thr | Cys | Lys | Phe | Val | Val | Asp | Asn | Leu | Tyr | Tyr | Ser | Thr | Asp | Tyr |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Glu | Phe | Leu | Val | Tyr | Phe | Tyr | Asn | Gly | Glu | Tyr | Leu | Gly | Asp | Pro | Glu |

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Leu Val Phe Leu Ile Ile Val Thr Ser Ile Ala Leu Leu Val Val Leu
                245                 250                 255
Tyr Lys Ile Tyr Asp Leu Arg Lys Lys Arg Ser Ser Asn Leu Asp Glu
            260                 265                 270
Gln Gln Glu Leu Val Glu Arg Asp Glu Glu Lys Gln Leu Ile Asn Val
        275                 280                 285
Asp Pro Ile His Ser Asp Leu Leu Leu Glu Thr Tyr Lys Arg Lys Ile
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Ala Asp Glu Gly Arg Leu Phe Leu Ala Glu Phe Gln Ser Ile Pro Arg
305                 310                 315                 320
Val Phe Ser Lys Phe Pro Ile Lys Asp Ala Arg Lys Ser Gln Asn Gln
                325                 330                 335
Asn Lys Asn Arg Tyr Val Asp Ile Leu Pro Tyr Asp Tyr Asn Arg Val
            340                 345                 350
Glu Leu Ser Glu Ile Asn Gly Asp Ala Gly Ser Thr Tyr Ile Asn Ala
        355                 360                 365
Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys Tyr Ile Ala Ala Gln
    370                 375                 380
Gly Pro Arg Asp Glu Thr Val Asp Asp Phe Trp Lys Met Ile Trp Glu
385                 390                 395                 400
Gln Lys Ala Thr Val Ile Val Met Val Thr Arg Cys Glu Glu Gly Asn
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Arg Asn Lys Cys Ala Glu Tyr Trp Pro Cys Met Glu Glu Gly Thr Arg
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Thr Phe Arg Asp Val Val Val Thr Ile Asn Asp His Lys Arg Cys Pro
        435                 440                 445
Asp Tyr Ile Ile Gln Lys Leu Ser Ile Ala His Lys Lys Glu Lys Ala
    450                 455                 460
Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr Ser Trp Pro Asp His
465                 470                 475                 480
Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys Leu Arg Arg Arg Val
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Asn Ala Phe Ser Asn Phe Phe Ser Gly Pro Ile Val Val His Cys Ser
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Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile Asp Ala Met Leu
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Glu Ser Leu Glu Ala Glu Gly Lys Val Asp Val Tyr Gly Tyr Val Val
    530                 535                 540
Asn Leu Arg Arg Gln Arg Cys Leu Met Val Gln Val Glu Ala Gln Tyr
545                 550                 555                 560
Ile Leu Ile His Gln Ala Leu Val Glu Tyr Asn Gln Phe Gly Glu Thr
                565                 570                 575
Glu Val Asn Leu Ser Glu Leu His Ser Cys Leu Gln Asn Leu Lys Lys
            580                 585                 590
Arg Asp Pro Pro Ser Asp Pro Ser Pro Leu Glu Ala Glu Tyr Gln Arg
        595                 600                 605
Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile Gly Asn Gln Glu
    610                 615                 620
Glu Asn Lys Lys Lys Asn Arg Ser Ser Asn Val Val Pro Tyr Asp Phe
625                 630                 635                 640
Asn Arg Val Pro Leu Lys His Glu Leu Glu Met Ser Lys Glu Ser Glu
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Ala Glu Ser Asp Glu Ser Ser Asp Glu Asp Ser Asp Ser Glu Glu Thr
            660                 665                 670
Ser Lys Tyr Ile Asn Ala Ser Phe Val Met Ser Tyr Trp Lys Pro Glu
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Met Met Ile Ala Ala Gln Gly Pro Leu Lys Glu Thr Ile Gly Asp Phe
690 695 700
Trp Gln Met Ile Phe Gln Arg Lys Val Lys Val Ile Val Met Leu Thr
705 710 715 720
Glu Leu Met Ser Gly Asp Gln Glu Val Cys Ala Gln Tyr Trp Gly Glu
725 730 735
Gly Lys Gln Thr Tyr Gly Asp Met Glu Val Met Leu Lys Asp Thr Asn
740 745 750
Lys Ser Ser Ala Tyr Ile Leu Arg Ala Phe Glu Leu Arg His Ser Lys
755 760 765
Arg Lys Glu Pro Arg Thr Val Tyr Gln Tyr Gln Cys Thr Thr Trp Lys
770 775 780
Gly Glu Glu Leu Pro Ala Glu Pro Lys Asp Leu Val Thr Leu Ile Gln
785 790 795 800
Asn Ile Lys Gln Lys Leu Pro Lys Ser Gly Ser Glu Gly Met Lys Tyr
805 810 815
His Lys His Ala Ser Ile Leu Val His Cys Arg Asp Gly Ser Gln Gln
820 825 830
Thr Gly Leu Phe Cys Ala Leu Phe Asn Leu Leu Glu Ser Ala Glu Thr
835 840 845
Glu Asp Val Val Asp Val Phe Gln Val Val Lys Ser Leu Arg Lys Ala
850 855 860
Arg Pro Gly Met Val Gly Ser Phe Glu Gln Tyr Gln Phe Leu Tyr Asp
865 870 875 880
Ile Met Ala Ser Ile Tyr Pro Thr Gln Asn Gly Gln Val Lys Lys Ala
885 890 895
Asn Ser Gln Asp Lys Ile Glu Phe His Asn Glu Val Asp Gly Ala Lys
900 905 910
Gln Asp Ala Asn Cys Val Gln Pro Ala Asp Pro Leu Asn Lys Ala Gln
915 920 925
Glu Asp Ser Lys Glu Val Gly Ala Ser Glu Pro Ala Ser Gly Ser Glu
930 935 940
Glu Pro Glu His Ser Ala Asn Gly Pro Met Ser Pro Ala Leu Thr Pro
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Ser Ser

<210> 86
<211> 2090
<212> DNA
<213> Homo sapiens

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<222> 2090
<223> n = A,T,C or G

<400> 86
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aaatggctgt atccccccccc taacctctcc ctgaccctgt atatagccca gccaggccca 2040
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<210> 87
<211> 595
<212> PRT
<213> Homo sapiens

<400> 87
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Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly Asp Gln
35 40 45
Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp Leu Tyr
50 55 60
Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr Tyr Thr
65 70 75 80
Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile His Leu
85 90 95
Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp Tyr His
100 105 110
Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala Lys Gly
115 120 125
Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro Gly Asp
130 135 140
Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro Gly Ser
145 150 155 160
Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly Arg Tyr
165 170 175
Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu Val Glu
180 185 190

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His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe Val Tyr
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Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp Ile Glu
    210                 215                 220
Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp Thr Ala
225                 230                 235                 240
Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln Glu Val
                245                 250                 255
Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn Lys Gly
            260                 265                 270
Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg Val Ile
        275                 280                 285
Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile Asn Ala
    290                 295                 300
Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala Lys Thr
305                 310                 315                 320
Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp Phe Trp
                325                 330                 335
Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr Thr Arg
            340                 345                 350
Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro Glu Val
        355                 360                 365
Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys Gly Glu
    370                 375                 380
His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser Pro Leu
385                 390                 395                 400
Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr Leu Ser
                405                 410                 415
Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu Ser Phe
            420                 425                 430
Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala Gly Pro
        435                 440                 445
Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr Ile Ile
    450                 455                 460
Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu Asp Cys
465                 470                 475                 480
Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln Arg Ser
                485                 490                 495
Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val Ala Ile
            500                 505                 510
Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu Gln Ser
        515                 520                 525
Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro Pro Ala
    530                 535                 540
Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys His Lys
545                 550                 555                 560
Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu Glu Lys
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Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Ser Lys Gly Ser Leu
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Lys Arg Lys
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<211> 2277
<212> DNA
<213> Homo sapiens

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<210> 89
<211> 597
<212> PRT
<213> Homo sapiens

<400> 89
Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala
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Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
20 25 30
Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
35 40 45
Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
65 70 75 80
Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile

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                85                  90                  95
His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
            100                 105                 110
Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
        115                 120                 125
Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
145                 150                 155                 160
Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
                165                 170                 175
Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
            180                 185                 190
Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
        195                 200                 205
Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
    210                 215                 220
Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
225                 230                 235                 240
Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln
                245                 250                 255
Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn
            260                 265                 270
Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg
        275                 280                 285
Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile
    290                 295                 300
Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala
305                 310                 315                 320
Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp
                325                 330                 335
Phe Trp Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr
            340                 345                 350
Thr Arg Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro
        355                 360                 365
Glu Val Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys
    370                 375                 380
Gly Glu His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser
385                 390                 395                 400
Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr
                405                 410                 415
Leu Ser Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu
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Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala
        435                 440                 445
Gly Pro Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr
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Ile Ile Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu
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Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln
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Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val
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Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu
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Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro
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Pro Ala Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys
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His Lys Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu
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<210> 90
<211> 2145
<212> DNA
<213> Homo sapiens

<400> 90

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<211> 595
<212> PRT
<213> Homo sapiens

<400> 91

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        35                  40                  45
Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp Leu Tyr
    50                  55                  60
Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr Tyr Thr
65                  70                  75                  80
Gln Gln Gln Gly Val Val Gln Asp Arg Asp Gly Thr Ile Ile His Leu
                85                  90                  95
Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp Tyr His
            100                 105                 110
Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala Lys Gly
        115                 120                 125
Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro Gly Asp
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Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly Arg Tyr
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Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu Val Glu
            180                 185                 190
His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe Val Tyr
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Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn Lys Gly
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Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg Val Ile
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Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile Asn Ala
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Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala Lys Thr
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Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr Thr Arg
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Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro Glu Val
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Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys Gly Glu
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His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser Pro Leu
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Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr Leu Ser
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Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu Ser Phe
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Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala Gly Pro
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Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr Ile Ile
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Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu Asp Cys
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Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val Ala Ile
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Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu Gln Ser
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Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro Pro Ala
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Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys His Lys
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Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu Glu Lys
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<211> 4301
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<223> n = A,T,C or G

<400> 92

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<212> DNA
<213> Homo sapiens

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<223> n = A,T,C or G

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Val Gln Thr Gln Glu Gln Tyr Glu Leu Val Tyr Ser Ala Val Leu Glu
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Leu Phe Lys Arg His Met Asp Val Ile Ser Asp Asn His Leu Gly Arg
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Lys Thr Thr Asn Gln His Ser Lys Gln Gly Ala Glu Ala Glu Ser Thr
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Pro Gly Lys Ser Phe Thr Arg Ser Lys Ser Leu Lys Ile Phe Arg Asn
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Met Lys Lys Ser Val Cys Asn Ser Ser Ser Pro Ser Lys Pro Thr Glu
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Arg Val Gln Pro Lys Asn Ser Ser Ser Phe Leu Asn Phe Gly Phe Gly
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Ser Leu Lys Arg Asn Ile Ser Leu Thr Pro Cys Arg Gly Leu Arg Trp
        595                 600                 605
Ala Asp Arg Asp Leu
    610
```

<210> 98
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Unique signature sequence motif found within
conserved domain

<221> VARIANT
<222> 1
<223> Xaa = Ile or Val

<221> VARIANT
<222> 4, 7, 8
<223> Xaa = Any Amino Acid

<221> VARIANT
<222> 10
<223> Xaa = Ser or Thr

<400> 98

```
Xaa His Cys Xaa Ala Gly Xaa Xaa Arg Xaa Gly
 1               5                  10
```